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PROGRESS IN ORGANIC CHEMISTRY

5

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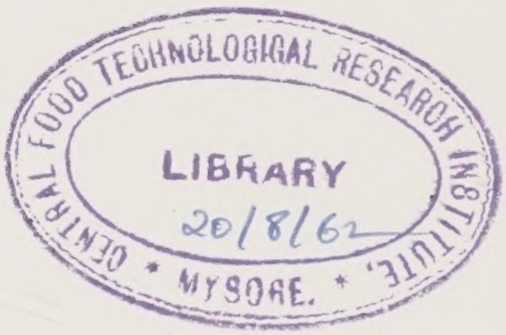

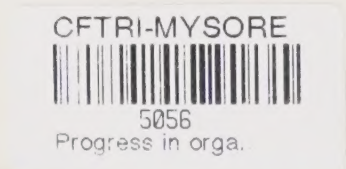

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FOREWORD

The growing volume of original research publications makes it increasingly difficult for the student of organic chemistry to keep himself informed about the important developments which are taking place in his subject. In many fields of research it is not easy for those who are actively contributing to be sure that they are fully acquainted with recent progress even in their own fields. It has become almost impossible for them to keep abreast, from the original literature, with developments in other fields as well. Hence short surveys of selected topics such as are given in the chapters of the volumes of this series are providing an increasingly important service for all who are interested in organic chemistry. Advanced university students, research workers and those whose interests are more general, are all indebted to the authors of these surveys, whose labours do much to facilitate the assimilation of knowledge of recent progress.

The chapters by Dr. Waters and Dr. Loudon are complementary. Dr. Waters gives an up-to-date account of oxidation reactions involving free radicals as intermediaries. His orderly and systematic treatment of the subject serves to emphasize the extent to which it is now possible to provide rational interpretations of a large variety of miscellaneous oxidation processes. Dr. Loudon's chapter deals more exhaustively with a limited aspect of the subject, and he gives a succinct and fascinating account of methods by which additional hydroxyl groups can be introduced into the aromatic nucleus of phenols.

Carbohydrate chemistry continues to attract the attention of many organic chemists, both for its intrinsic interest and also because of the important part which substances of this group play in Nature and in natural processes. Dr. Ricketts has given a valuable review of recent work on the chemistry and biochemistry, including the biosynthesis, of dextran, a medicinally important carbohydrate produced by some of the lower organisms.

To the natural products chemist the chapter on the higher terpenoids will have outstanding appeal. From the earliest days of structural organic chemistry the terpenes and their derivatives have had a fascination of their own which has progressively increased as their ramifications and their inter-relationships have been steadily unfolded. Dr. Barltrop and Dr. Rogers have confined their treatment

of recent chemical progress very largely to the diterpenoids, the knowledge of which has been impressively advanced in recent years. Not the least important achievement has been the elucidation of the stereochemical configuration of many members of this group, revealing a beautiful simplicity of pattern; but the most exciting part of this chapter is the final section dealing with terpene biogenesis. The problem of how the complex polycyclic structures present in the higher terpenoids and in the steroids have been elaborated from simple units seems to have been largely solved, thanks mainly to the use of isotopic tracers. The relationship between the higher terpenoids and the steroids, long suspected but difficult to reconcile wholly with their structural differences, has been placed on a firm experimental basis.

Among the quasi-aromatic compounds having non-benzenoid structures those related to cycloheptatrienone are the most extensively investigated and probably the most important. Fifteen years ago they represented an unknown field of organic chemistry, now they have found a permanent place in the classification of organic compounds, and some forty of them have been found in Nature. Professor Nozoe, himself a prolific worker in this field, gives in the last chapter of this book a lucid and systematic survey of the properties, structural relationships and methods of synthesis of tropylium salts, tropolones and related compounds.

I am greatly indebted to the authors for their co-operation in the preparation of these authoritative essays of topical chemical interest, and I wish also to express my appreciation of the collaboration of Dr. W. Carruthers who has rendered invaluable assistance as Joint Editor of this volume.

J. W. Cook

1

HOMOLYTIC OXIDATION PROCESSES

W. A. Waters

THE ELECTRONIC THEORY OF OXIDATION

INORGANIC chemists are accustomed to use the terms *oxidation* and *reduction* for reactions whereby electrons are removed from, or added to, molecules or ions; *e.g.*

$$Fe^{2+} \underset{Reduction}{\overset{Oxidation}{\rightleftharpoons}} Fe^{3+} + e$$

and, since they frequently deal with rapid reversible reactions, they often compare oxidizing agents in terms of their redox potentials, E_0, measured with reference to the normal hydrogen electrode. Biochemical oxidations involving enzyme catalysts, again being thermodynamically reversible, are often treated in a similar way though the appropriate potential (E_0'), for obvious convenience, refers to reactions in neutral solution.

To organic chemists, however, this potentiometric classification of oxidizing agents is seldom of obvious value, since few oxidations of organic compounds are reversible reactions.

In general, organic molecules have a carbon skeleton surrounded by a hydrogen skin attached by very strong covalences (the C—H bond strength is about 95 kcal) and have more weakly bound electrons available for removal only at the π-electron sites of olefins, or at atoms, such as oxygen, nitrogen or sulphur near which unshared pairs may be localized. It is at, or near, these groups which have accessible electrons that oxidations of organic molecules most easily occur. Wieland's generalization[1] of over 40 years ago to the effect that in organic chemistry 'oxidation' and 'reduction' were equivalent to *hydrogen removal* and *hydrogen addition*, respectively, is a tacit recognition of this difficulty of abstraction of electrons from organic molecules and is still a valuable dictum, provided that it is recognized that the oxidative removal of hydrogen from an organic molecule requires the abstraction of both a hydrogen nucleus and an electron, e.g.

$$CH_3—CH_2—OH \longrightarrow CH_3—CH{=}O + 2H^+ + 2e$$

and not that of the hydrogen nucleus alone, as in an ionization:

$$CH_3—CH_2—O—H \longrightarrow (CH_3—CH_2—O{:})^- + H^+$$

Oxidations of organic molecules, like all other reactions of covalent molecules, involve electron-pair-bond rupture, and this may be effected either by heterolyses in which two electrons are removed in a single process, or by homolyses in which single electrons are removed in each of two consecutive reactions.

Nearly all heterolytic oxidation processes are recognizable additions or eliminations involving polar electrophilic reagents, while homolytic oxidations, since they sever electron pairs, necessarily involve the transient production of free radicals which can often be detected.

Homolytic oxidation can be effected either by hydrogen atom removal, e.g.

$$CH_3—CH_2—OH + \cdot OH \longrightarrow CH_3\cdot\dot{C}H—OH + H—OH$$

or merely by electron removal, e.g.

$$(Me—C_6H_4—O{:})^- + \{Fe(CN)_6\}^{3-} \longrightarrow Me—C_6H_4—O\cdot + \{Fe(CN)_6\}^{4-}$$

and can be divided into two groups, according to whether the oxidant is a hydrogen-atom-abstracting agent or merely an electron abstractor. Active free atoms, such as chlorine, and active free radicals, such as $\cdot OH$, $\cdot C_6H_5$ or $\cdot CH_3$, together with the molecules from which they may be generated (e.g. benzoyl peroxide), fall into the first group, while ions of the higher valence states of many transition elements, e.g. Co^{3+}, Mn^{3+}, Fe^{3+}, Ce^{4+}, are oxidants of the second group. However, many oxidations of organic compounds now appear to be concerted electron removal processes in which it may be difficult to decide whether the bond fissions are of heterolytic or homolytic type. Some reagents, such as the halogens and the organic peroxides, can act both in heterolytic and in homolytic fashion according to the chemical nature of the solvents involved, and again there are complex inorganic oxidants, such as chromic acid and potassium permanganate, which may act consecutively in both heterolytic and homolytic manner. So, in the following pages, all that can be done is to illustrate the more typical features of homolytic electron removal.

HOMOLYTIC OXIDATIONS INVOLVING HYDROGEN ABSTRACTION

Homolytic Halogenation

The atomic chlorination of an organic compound

$$(1) \qquad R{-}CH_3 + \cdot Cl \longrightarrow R{-}CH_2\cdot + H{-}Cl$$

$$(2) \qquad R{-}CH_2\cdot + Cl_2 \longrightarrow R{-}CH_2{-}Cl + \cdot Cl$$

may be regarded as an oxidation since it leads, by subsequent hydrolysis,

$$(3) \qquad R{-}CH_2{-}Cl + NaOH \longrightarrow R{-}CH_2{-}OH + NaCl$$

to the formation of an oxidized derivative of the original compound. This is of technical importance for the side-chain oxidation of toluene but is of little general applicability, for the following reason. Reaction (1) is exothermic even for methane, and consequently reagents that can supply chlorine atoms, as for example chlorine gas activated by light, or sulphuryl chloride activated by free radicals produced thermally from benzoyl peroxide or, better, $\alpha\alpha'$-azobis-isobutyronitrile[2], effect chlorination of all positions in the higher paraffins, giving mixtures which have been regarded as intractable prior to the elaboration of methods of vapour-phase chromatography.

Now, however, it is clear that atomic chlorination does show some degree of *relative* selectivity[3]. Thus for attack on C—H groups of paraffins the relative orders of reactivity, at room temperature, are approximately *tertiary : secondary : primary* = 5:4:1 but they become more alike as the temperature of reaction increases[3,4]. For dichlorination there is a marked tendency for the second chlorine atom to attack either another hydrogen atom on the carbon which already has been halogenated or a C—H bond remote from the chlorine atom previously introduced. Again, in the chlorination of butyric acid the relative percentages of attack are

$$\underset{45}{CH_3}—\underset{45}{CH_2}—\underset{10}{CH_2}—CO_2H \qquad \text{with sulphuryl chloride}[5]$$

$$\underset{31}{CH_3}—\underset{64}{CH_2}—\underset{5}{CH_2}—CO_2H \qquad \text{with irradiated chlorine}[6].$$

Reaction (1) above involves the formation of a strongly dipolar molecule, H—Cl, and in the course of the C—H bond fission there is, consequently, an electron displacement away from the carbon centre. Hence groups, R, which are electrophilic should tend to decrease the ease of homolytic chlorination, and vice versa. Brown[7] has arranged substituents R, in $R—CH_2—$, in the following order in respect to their influence on the relative rates of atomic chlorination of the $—CH_2—$ group

$$CH_3 > H > ClCH_2 > Cl_2CH > HO{\cdot}CO > Cl_3C > F_3C$$

and comments that the order indicates a control of the reactivity by an inductive effect.

Recently, it has been shown by Russell that homolytic chlorination becomes a more selective reaction if it is carried out in an aromatic solvent such as benzene[8], and still more selective if carbon disulphide is used.

Table I indicates the magnitude of this solvent effect.
He suggests that the aromatic solvent forms a π-complex with the atomic chlorine, with the consequence that the thermochemistry of a liquid phase reaction (1) is no longer the same as that for the gas phase reaction, but involves a chlorine atom with lower intrinsic energy and leads to the production of a solvated organic radical[9].

Table I. Relative Reactivities of C—H *bonds towards Chlorine Atoms at* 40°C

(By courtesy of the American Chemical Society[8])

Hydrocarbon	*Hydrogen in*	'*Free* Cl·'	Cl· *in benzene*	Cl· *in* CS_2
2:3-*Dimethyl-pentane*	CH_3	1*	1*	1*
	CH	3·9	16	200
Cyclopentane	CH_2	2·8	5·2	23
Cyclohexane	CH_2	2·7	5·2	20
Chloroform	CH	0·005	—	0·033
Toluene	CH_3	1·1	2·1	11

* Assumed as the standard

In contrast to chlorination, photochemical bromination is highly selective[3] and is an excellent method for the preparation of tertiary bromides from appropriate paraffins. Russell and Brown[10] have found that, at 80° C, toluene is 60 times as reactive as cyclohexane towards bromine atoms, whereas towards chlorine atoms cyclohexane is 11 times as reactive as toluene. They ascribe this marked change to the difference in degree of bond breaking which is needed in reaching the transition states (*a*) and (*b*) in which the colliding particles have gained enough activation energy for hydrogen transfer to occur.

(*a*) R″CH · · · · H · · · · Cl (*b*) R″CH · · · · H · · · · Br

Homolytic chlorination (equation 1) is so exothermic that the degree of bond extension in reaching the energy peak (*a*) from the original molecule, R″CH—H, need not be large before the progressive energy gain in forming the final molecule, H—Cl·, helps the reaction forward. Consequently the chemical structure of molecule R″CH—H is not very important in controlling the energy level of transition state (*a*). The bond strength of H—Br, however, is so much less than that of H—Cl that, in arriving at transition state (*b*), a much greater degree of stretching of the C—H bond is needed than in case (*a*), and hence the energy level of (*b*) will depend to a considerable extent upon the energy difference between the structures of the molecule R″CH—H and of the eventual carbon radical R″CH·. Thus while, in the main, the course of homolytic chlorination of aliphatic molecules is controlled by inductive effects, for homolytic bromination the major controlling factor is the degree of resonance stabilization of the resulting organic

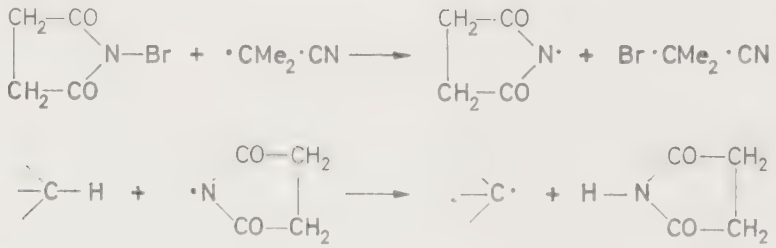
free radical. In consequence, homolytic bromination shows sufficient selectivity to be applicable as a route for the specific oxidation of complex molecules at desired points.

With alkylbenzenes the attack is exclusively upon α—C—H groups since resonance-stabilized benzyl radicals then result. With allylic systems the reaction (4)

$$(4)\quad Br\cdot + A{-}CH_2{-}CH{=}CH{-}B \longrightarrow$$

$$HBr + A{-}\dot{C}H{-}CH{=}CH{-}B \longleftrightarrow A{-}CH{=}CH{-}\dot{C}H{-}B$$

is exothermic and irreversible, while the thermochemistry of bromine atom addition to the C=C bond is so evenly balanced that the reaction is reversible, the ease of the addition or the dissociation of the bromine atom depending upon whether the *cis* or the *trans* isomer of the olefin is involved[11]. Molecular bromine, however, can easily effect heterolytic addition to olefins and consequently, to effect allylic bromination of a compound A—CH_2—CH=CH—B, bromine *atoms* should slowly be supplied at very low concentration so that reaction (4) can be the rate-controlling process. This can be done by adding bromine very slowly to a hot, irradiated solution of the olefin in a non-ionizing solvent[12] or by using a suspension of N-bromosuccinimide in a similar solvent together with a radical-producing catalyst, such as $\alpha\alpha'$-azobisisobutyronitrile, which has no undesired oxidizing action itself[13]. Under the latter conditions the real dehydrogenating agent is the succinimido radical (I).



I

To effect allylic bromination with N-bromo succinimide, care must be taken not to use an acidic solvent or catalyst, for the cation (II) reacts heterolytically, transferring a bromine cation to the double bond of an olefin or substituting bromine into an activated aromatic nucleus.

II

Oxidation by Oxy-radicals, R—O·

(a) *Free hydroxyl*—Since the energy needed to remove the first hydrogen atom from a molecule of water is about 140 kcal/mole, free hydroxyl radicals are the most powerful of known oxidizing agents. They can easily be produced in water by one-electron abstraction from hydrogen peroxide, e.g.

(5) $$Fe^{2+} + HO—OH \longrightarrow (Fe—OH)^{2+} + \cdot OH$$

by rupture of water molecules by ionizing radiations such as X-rays, γ-rays or neutrons

(6) $$H_2O \rightsquigarrow (H_2O)^+ + e \; : \; (H_2O)^+ \longrightarrow H^+ + \cdot OH$$

or from ions of some transition metals by photochemical excitation, using radiation of wavelengths corresponding to charge-transfer absorption bands[14], e.g.

(7) $$(Fe—OH)^{2+} + h\nu \longrightarrow Fe^{2+} + \cdot OH$$

However generated, free hydroxyl radicals are dehydrogenators with little selectivity towards C—H bonds, for they attack alcohols, ethers, esters and even saturated aliphatic acids, though the ensuing reactions of the resulting organic free radicals differ to a wide degree.

For example, hydroxyl radicals generated by Fenton's reagent (hydrogen peroxide together with a ferrous salt) as in equation (5) react with primary or secondary alcohols to produce organic radicals which are strong reducing agents, capable[15] of converting Fe^{3+} to Fe^{2+} or Hg^{2+} to Hg^{+}. Consequently the sequence of reactions (5), (8) and (9) is a reaction chain whereby alcohol can be oxidized to aldehyde with little net consumption of Fe^{2+}

(8) $$HO\cdot + CH_3—CH_2—OH \longrightarrow HO—H + CH_3—\dot{C}H—OH$$

(9) $$CH_3—\dot{C}H—OH + Fe^{3+} \longrightarrow CH_3—CH{=}O + H^+ + Fe^{2+}$$

though reaction (9) can be eliminated by adding a suitable complexing agent, such as fluoride, to remove the secondary oxidant, Fe^{3+}, from the solution[15,16]. Reactions such as (8) and (9) are used to advantage in many technical recipes for effecting the emulsion polymerization of olefins. In this type of polymerization, active radicals are generated from the olefins by the addition of hydroxyl radicals or of $\cdot SO_4H$ radicals generated similarly from sodium persulphate, and it is advisable to keep the concentration of Fe^{3+} to a low value, since one-electron oxidations, such as (11), are effective chain-terminating reactions[17].

(10) $HO\cdot + CH_2{=}CH{\cdot}R \longrightarrow HO{-}CH_2{-}\dot{C}H{-}R$

(11) $HO{-}(CH_2{-}CHR)_n{-}CH_2{-}\dot{C}HR + Fe^{3+} \longrightarrow HO{-}(CH_2{-}CHR)_n{-}CH{=}CHR + H^+ + Fe^{2+}$

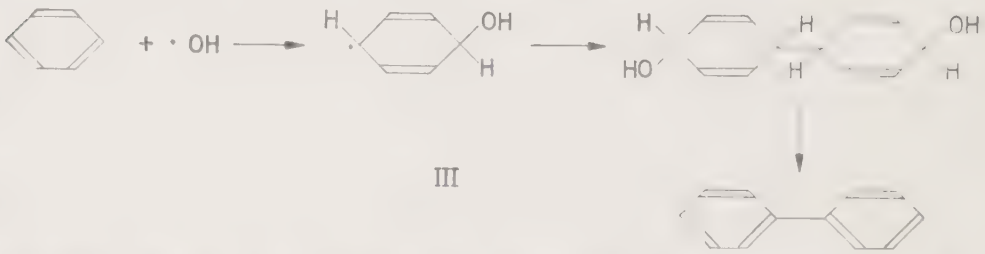
The induction of olefin polymerization (reaction 10) and the secondary reduction of a weak oxidizer during the progress of another oxidation reaction (reactions 9 or 12)

(12) $CH_3{-}\dot{C}H{-}OH + Hg^{2+} \longrightarrow CH_3{-}CH{=}O + Hg^{+} + H^{+}$

can both be used as diagnostic tests of homolytic oxidation.

There are, however, many organic free radicals which are too weak as reducing agents to react[16] with Fe^{3+} or Hg^{2+} and a very few free radicals, e.g. $\cdot CH(CO_2H)_2$, which even seem to be oxidizing agents[18].

For instance, the oxidations of aliphatic acids and esters are not chain reactions[15] and, under most conditions, neither is the reaction with benzene[19]. In this case it is probable that the primary reaction of free hydroxyl is an addition



to give a radical (III) which then dimerizes and loses water to form diphenyl, but if Fe^{3+} is present in very high concentration some phenol is formed

(13) 

while with high concentrations of Fe^{2+} some benzene is regenerated[20].

(14) $$(\cdot C_6H_6—OH) + Fe^{2+} \longrightarrow C_6H_6 + (HO:)^- + Fe^{3+}$$

Complications due to the concurrent presence of different oxidizing and reducing agents also beset the oxidation of organic compounds that can be induced in water by ionizing radiations. While unstable $(H_2O)^+$ cations break to give hydroxyl radicals (equation 6), electrons can disrupt water molecules to yield hydrogen atoms

(15) $$e + H_2O \longrightarrow (H_2O)^- \longrightarrow H\cdot + (:OH)^-$$

and if the water contains dissolved air, this then reacts to give peroxy radicals.

(16) $$H\cdot + O=O \longrightarrow H—O—O\cdot$$

Since even hydrogen atoms can sometimes act as oxidizing agents[21]

(17) $$R—H + \cdot H \longrightarrow R\cdot + H_2$$

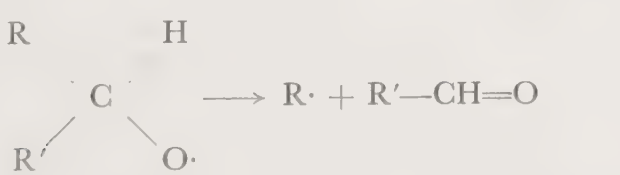
it is not surprising that radiochemical decompositions of aqueous solutions of organic compounds are, on the whole, oxidations of quite a complex character. The biochemical implications of such reactions are important, for electron transfer processes such as those of equations (6) and (15) can be effected within living cells.

(*b*) *Alkyloxy radicals*—Reducing ions, such as Fe^{2+} and Co^{2+}, also split alkyl hydroperoxides, R—O—O—H, homolytically, but invariably give alkyloxy radicals, R—O·, and not hydroxyl, i.e.

(18) $$R—O—O—H + Fe^{2+} \longrightarrow R—O\cdot + (Fe—OH)^{2+}$$

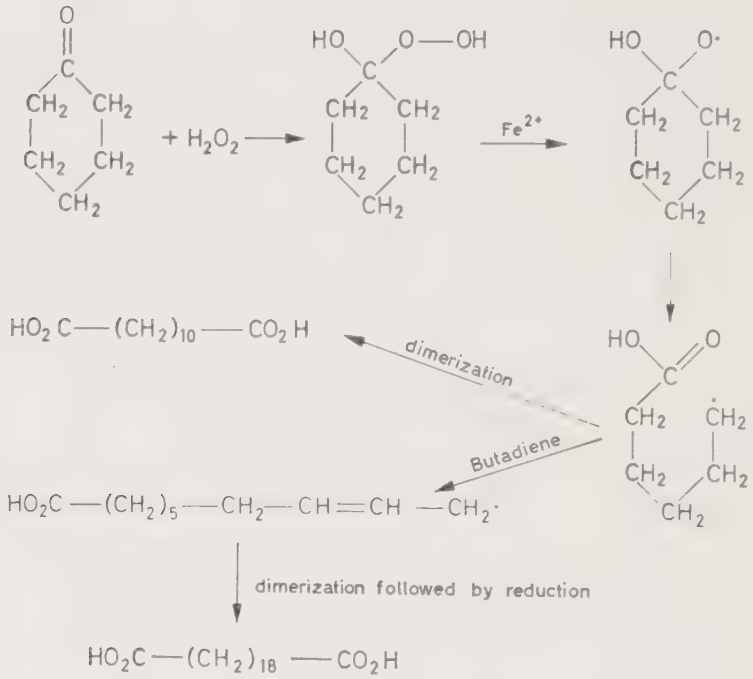
Alkyloxy radicals, though they have a sufficiently long free life to be detected as end-groups of polymers formed by additions to olefins, tend to break down on heating to carbonyl derivatives and alkyl radicals:

(19) $$R—CH_2—O\cdot \longrightarrow R\cdot + CH_2=O$$

(20)


(21) $$R_3C—O\cdot \longrightarrow R\cdot + R_2C=O$$

This thermal degradation has a very important role in the gas phase oxidation of hydrocarbons[22,23]. The following reactions exemplify the synthetic potentialities of oxidations of this type[24].



Alkyloxy radicals are also generated by the thermal decomposition of dialkyl peroxides, alkyl hypochlorites, alkyl nitrites or alkyl nitrates, e.g.

(22) $(CH_3)_3C-O-O-C(CH_3)_3 \longrightarrow 2(CH_3)_3C-O\cdot$

(23) $C_8H_{17}-O-N=O \longrightarrow C_8H_{17}-O\cdot + \cdot N=O$

(24) $C_2H_5-O-NO_2 \longrightarrow C_2H_5-O\cdot + \cdot NO_2$

(25) $(CH_3)_3C-O-Cl \longrightarrow (CH_3)_3C-O\cdot + \cdot Cl$

and the chemistry of these decompositions has been reviewed by Gray and Williams[23]. Since the subsequent decompositions (reactions 19 and 20) of primary and secondary alkyloxy radicals occur very easily indeed, these thermal decompositions are reactions which are highly exothermic and often of explosive character. For instance, a homolysis

like (24) probably initiates the detonation of nitroglycerol. Again, t-butyl hypochlorite is a controllable homolytic chlorinating agent[25].

$$\left.\begin{array}{lll} (26) & (CH_3)_3C{-}O\cdot + H{-}R \longrightarrow (CH_3)_3C{-}OH + R\cdot \\ (27) & R\cdot + (CH_3)_3COCl \longrightarrow RCl + (CH_3)_3CO\cdot \end{array}\right\}$$

The thermal decomposition of ditertiary butyl peroxide (22), however, occurs controllably at 110–150° when the peroxide is refluxed in suitable solvents of this boiling range. Since both t-butoxy radicals, $(CH_3)_3C{-}O\cdot$ and the methyl radicals generated from them by the decomposition (21), are dehydrogenating agents, this peroxide is a valuable homolytic oxidant. For instance, the decomposition of di-t-butyl peroxide in boiling toluene generates benzyl radicals almost quantitatively. Though these rapidly combine to form dibenzyl, the reacting toluene solution can be used to benzylate active polycyclic aromatic or heterocyclic compounds such as anthracene or acridine[26]. The removal of α-hydrogen atoms from aromatic side chains in this way has been studied quantitatively by JOHNSTON and WILLIAMS[27]. By carrying out the dehydrogenations

$$(26)\quad (CH_3)_3C{-}O\cdot + CH_3{-}Ar \longrightarrow (CH_3)_3C{-}OH + \cdot CH_2{-}Ar$$

$$(28)\quad Ar{-}CH_2\cdot + \cdot CH_2{-}Ar' \longrightarrow Ar{-}CH_2{-}CH_2{-}Ar'$$

in a mixture of two solvents, $CH_3{-}Ar$ and $CH_3{-}C_5H_4N$ (γ-picoline), and analysing the resulting mixture of dimers they have shown that hydrogen abstraction by alkyloxy radicals, like hydrogen abstraction by chlorine atoms (see p. 5), does involve some degree of polarization in the transition state. Similar conclusions have been reached by HUANG[28] from studies of dehydrogenations by t-butoxy radicals of unsymmetrical benzyl ethers, $Ar{\cdot}CH_2{-}O{-}CH_2{\cdot}Ar'$, though in these molecules the main deciding factor is the degree of resonance stabilization of the resulting free radical.

t-Butoxy radicals react in a similar way with aliphatic amines; these are dehydrogenated at C—H groups adjacent to their nitrogen atoms[29].

Dehydrogenations of aldehydes are of interest, as the radicals formed from aliphatic aldehydes lose carbon monoxide at temperatures over

100°, and there is then set up a reaction chain[30] which may be further catalysed by the addition of a small amount of a thiol[31].

(26) $Me_3C—O\cdot + R—CHO \longrightarrow Me_3C—OH + R—CO\cdot$

(29) $\left\{ \begin{array}{l} R—CO\cdot \longrightarrow R\cdot + CO \\ \\ R\cdot + R—CHO \longrightarrow R—H + R—CO\cdot \end{array} \right.$

Benzaldehyde, however, gives the resonance-stabilized radical Ph—CO· which adds on to the oxygen atom of another benzaldehyde molecule[32].

$$Ph—CHO + Ph—CO\cdot \longrightarrow Ph—\dot{C}H—O—CO—Ph \longrightarrow \begin{array}{l} Ph—CH—O—CO—Ph \\ \quad\quad | \\ Ph—CH—O—CO—Ph \end{array}$$

Alkyloxy radicals can be formed by metallic-ion-catalysed reactions of per-esters as well as of hydroperoxides. t-Butyl-perbenzoate has recently been used together with a trace of a copper or cobalt salt to attack C—H groups adjacent to olefinic bonds without causing any rearrangement of the olefinic system[33]. The reaction with octene-1 has been represented as follows

(30) $Ph\cdot CO\cdot O—O\cdot CMe_3 + Cu^+ \longrightarrow (Ph\cdot CO\cdot O\ Cu)^- + \cdot OCMe_3$

(26) $Me_3C—O\cdot + H—R \longrightarrow Me_3C—OH + R\cdot$

(31) $R\cdot + (Ph\cdot CO—O\ Cu)^+ \longrightarrow Ph\cdot CO\cdot O—R + Cu^+$

where processes (26) and (31) are thought to be concerted. However, $(Ph\cdot CO\cdot O\ Cu)^+$ is really an ion pair, i.e. $(Ph—CO\cdot O:)^-$, Cu^{2+} and equation (31) may well comprise the reactions below (see p. 7)

$$\left. \begin{array}{l} R\cdot + Cu^{2+} \longrightarrow R^+ + Cu^+ \\ \\ R^+ + (Ph\cdot CO\cdot O:)^- \longrightarrow Ph\cdot CO—O—R \end{array} \right\}$$

though the complete absence of primary allylic benzoates from reactions of terminal olefins shows that neither *free* radical, (R·), nor *free* carbonium ion, (R^+), intermediates can be liberated in catalysed oxidations of this type.

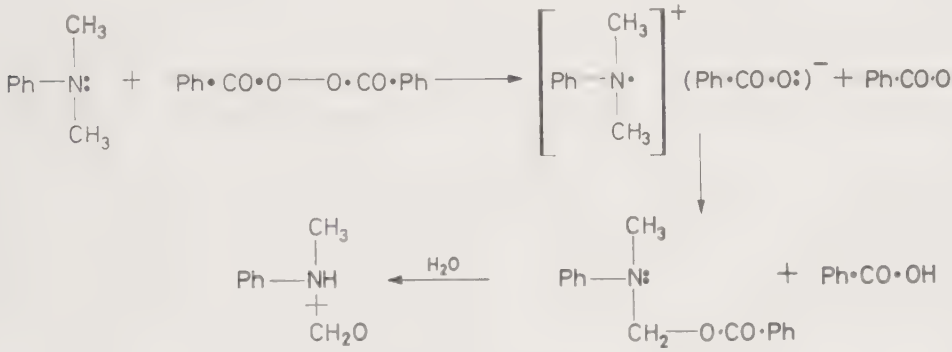
(c) *Acyloxy radicals*, R·CO·O·—The thermal decomposition of diacyl peroxides, such as benzoyl peroxide, is the best known method for generating free radicals, but the decomposition is, in part, a chain reaction[34]

(32) $Ph{\cdot}CO{\cdot}O{-}O{\cdot}CO{\cdot}Ph \rightleftharpoons 2\ Ph{\cdot}CO{\cdot}O{\cdot}$

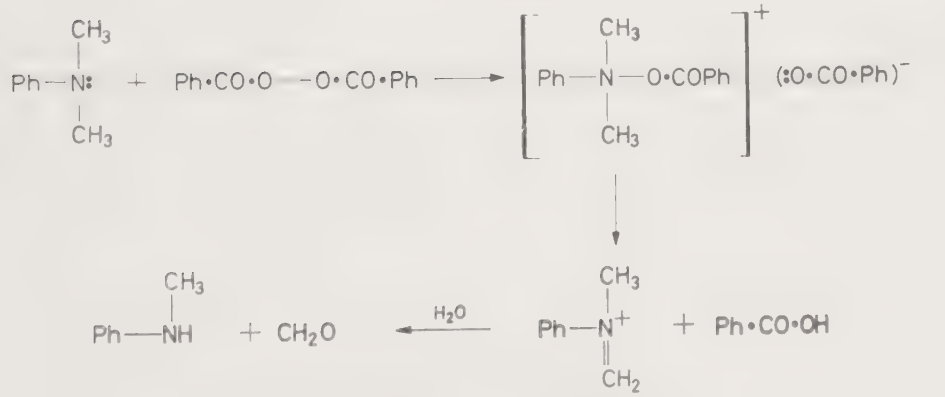
(33) $Ph{\cdot}CO{\cdot}O{\cdot} \longrightarrow Ph{\cdot} + CO_2$

(34) $Ph{\cdot} + Ph{\cdot}CO{\cdot}O{-}O{\cdot}CO{\cdot}Ph \longrightarrow Ph{\cdot}O{\cdot}CO{\cdot}Ph + Ph{\cdot}CO{\cdot}O{\cdot}$

and also may, in polar solvents, or under the influence of strong acid or base catalysts, take a heterolytic course[35]. For the latter reason it is now considered that a number of oxidations effected by benzoyl peroxide, and once thought to be homolytic processes, e.g. the oxidations of certain phenols[36] and arylamines, may not involve free radicals. For instance, the reaction between dimethylaniline and benzoyl peroxide can be interpreted in both the following ways[37].



Homolytic Reactions



Heterolytic Reactions of the Amine-oxide.

There is a similar uncertainty in regard to oxidations effected by lead tetra-acetate, which may liberate acetoxy free radicals, $CH_3{\cdot}CO{\cdot}O{\cdot}$, when heated in non-polar solvents such as benzene, but can react heterolytically at lower temperatures and in polar solvents.

Since benzoyl peroxide can generate two different radicals, viz. highly active free phenyl, Ph·, and resonance-stabilized benzoyloxy, $Ph{\cdot}CO{\cdot}O{\cdot}$, there is often doubt as to the nature of the real radical oxidant. With the less stable peroxides of aliphatic acids, such as acetyl peroxide, there is much less doubt in regard to reaction mechanisms, for aliphatic radicals, such as acetoxy, $CH_3{\cdot}CO{\cdot}O{\cdot}$, lose carbon dioxide so rapidly and so quantitatively that their dehydrogenating actions are undoubtedly due to free alkyl radicals. Methyl radicals generated in this way from acetyl peroxide have been used by SZWARC and his colleagues[38] to compare the strengths of C—H bonds in different molecules, and also the relative rates of homolytic methylation of series of olefins and of aromatic compounds. In general, aliphatic molecules are dehydrogenated, while aromatic molecules are methylated though not often with high efficiency[38].

These oxidations of aliphatic molecules by diacyl peroxides show some selectivity, since benzoyl peroxide and acetyl peroxide both attack with ease the hydrogen atoms of the —CHO groups of aldehydes, C—H bonds of the carbinol groups ($\cdot CH_2$—OH, :CH—OH) of primary and secondary alcohols[39], and C—H bonds adjacent to the oxygen atoms of ethers[40] or to the nitrogen atoms of aliphatic amines[41]. Tertiary alcohols behave like ethers in being attacked, though with difficulty, at C—H bonds adjacent to the oxygen atom[39].

Often chain reactions can be set up, and solvents may unexpectedly act as secondary oxidants. The following chain reaction[42,43] is noteworthy since carbon tetrachloride is not usually regarded as an oxidizing agent.

$$(35)\quad Ph{\cdot}CO{\cdot}O{\cdot} + Me_2CH{-}OH \longrightarrow Ph{\cdot}CO{\cdot}OH + Me_2\dot{C}{-}OH$$

$$(36)\quad \begin{cases} Me_2C{-}OH + CCl_4 \longrightarrow Me_2C{=}O + HCl + {\cdot}CCl_3 \\ Me_2CH{-}OH + {\cdot}CCl_3 \longrightarrow Me_2\dot{C}{-}OH + H{-}CCl_3 \end{cases}$$

The oxidation by carbon tetrachloride of triethyl phosphite is a similar chain reaction[44].

$$(37)\quad \begin{cases} :P(OEt)_3 + \cdot CCl_3 \longrightarrow Cl_3C{-}\dot{P}(OEt)_3 \longrightarrow \\ \qquad\qquad\qquad\qquad\qquad\qquad Cl_3C{-}\underset{\underset{O}{\|}}{P}(OEt)_2 + \cdot Et \\ CCl_4 + \cdot Et \longrightarrow Et{-}Cl + \cdot CCl_3 \end{cases}$$

Such reactions serve to show that highly chlorinated aliphatic compounds cannot safely be used as inert solvents in homolytic reactions. Nitrobenzene is another liquid which can act as a secondary homolytic oxidant[15].

In common with reactions of hydrogen peroxide, reactions of diacyl peroxides can be catalysed by metals such as copper or mercury and also by cuprous or cobaltous salts[43]. Thus copper catalyses the oxidation of methanol by benzoyl peroxide:

$$(38)\quad Ph{\cdot}CO{\cdot}O{-}O{\cdot}CO{\cdot}Ph + Cu \longrightarrow (Ph{\cdot}CO{\cdot}O:)^- Cu^+ + Ph{\cdot}CO{\cdot}O{\cdot}$$

$$(35)\quad Ph{\cdot}CO{\cdot}O{\cdot} + CH_3OH \longrightarrow Ph{\cdot}CO{\cdot}OH + \cdot CH_2OH$$

Unsymmetrical diacyl peroxides, naturally, split to give the products of less reactivity[43], e.g.

$$(39)\quad \begin{cases} Ph{\cdot}CO{\cdot}O{-}O{\cdot}CO{\cdot}CH_2{\cdot}Ph + Cu \longrightarrow (Ph{\cdot}CO{\cdot}O:)^- Cu^+ + Ph{\cdot}CH_2{\cdot}CO{\cdot}O{\cdot} \\ Ph{\cdot}CH_2{\cdot}CO{\cdot}O \longrightarrow CO_2 + Ph{\cdot}CH_2{\cdot} \longrightarrow Ph{\cdot}CH_2{\cdot}CH_2{\cdot}Ph \end{cases}$$

(d) Alkylperoxy radicals, R–O–O· —Alkylperoxy radicals may be generated (*i*) by the addition of oxygen to free alkyl radicals: this occurs in autoxidation processes which are discussed in detail below, and (*ii*) by the one-electron oxidation of alkyl hydroperoxides, R—O—O—H. Arylperoxy radicals, e.g. Ph—O—O·, which may be formed in the reactions of oxygen with aromatic Grignard reagents[46], have as yet been little explored.

Just as hydrogen peroxide can be oxidized quantitatively to oxygen by ceric, manganic or cobaltic ions (amongst others) by two-stage reactions

$$(40)\quad H_2O_2 \rightleftharpoons (HO_2:)^- + H^+$$
$$(HO_2:)^- + Ce^{4+} \rightarrow HO{\cdot}O{\cdot} + Ce^{3+}$$

$$(41)\quad H{\cdot}O{\cdot}O{\cdot} \rightleftharpoons H^+ + (—O—O:)^-$$
$$(\cdot O—O:)^- + Ce^{4+} \rightarrow O_2 + Ce^{3+}$$

so alkyl hydroperoxides can be converted to alcohols, the final reactions being of the type[47]

(42) $\mathrm{R{-}O{-}O\cdot + Ce^{4+} \longrightarrow R^+ + O_2 + Ce^{3+}}$

(43) $\mathrm{R^+ + H_2O \longrightarrow R{-}OH + H^+}$

While R—O· radicals are strong oxidants, R—O—O· radicals are both weak oxidizing and weak reducing agents. As explained below, the reaction

(44) $\mathrm{R{-}O{-}O\cdot + H{-}R' \longrightarrow R{-}O{-}O{-}H + \cdot R'}$

is endothermic unless the radical R′· is a resonance-stabilized system, and in general RO_2· radicals do not attack the C—H bonds of paraffin chains or of the carbinol groups of alcohols.

They can, however, add easily to free alkyl radicals, R′·, and slowly to C=C bonds of some olefins. Of the few such reactions that have been elucidated clearly, the following, due to KHARASCH and his colleagues, are of recent interest[48]:

(18) $\mathrm{Me_3C{-}O{-}OH + Co^{2+} \longrightarrow Me_3C{-}O\cdot + Co^{3+} + (:OH)^-}$

(40) $\mathrm{Me_3C{-}O{-}OH + Co^{3+} \longrightarrow Me_3C{-}O{-}O\cdot + Co^{2+} + H^+}$

(45) $\mathrm{C_5H_{11}{-}CH_2{-}CH{=}CH_2}$ (octene-1) $\mathrm{+ Me_3C{-}O{-}O\cdot \longrightarrow}$

$$\mathrm{C_5H_{11}{-}CH_2{-}\dot{C}H{-}CH_2{-}O{-}O{-}CMe_3}$$

(11) $\mathrm{C_5H_{11}{-}CH_2{-}\dot{C}H{-}CH_2{-}O{-}O{-}CMe_3 + Co^{3+}}$

$$\longrightarrow \mathrm{C_5H_{11}{-}CH{=}CH{-}CH_2{-}O{-}O{-}CMe_3 + H^+ + Co^{2+}}$$

A small percentage of cobaltous acetate suffices and no isomeric peroxide

$$\mathrm{C_5H_{11}{-}CH(O{-}O{-}CMe_3){-}CH{=}CH_2}$$

is formed.

Analogous reactions carried out in the presence of traces of cupric salts have given quite different results[49] and, in the above reaction sequence, it may be possible that the cobaltic ion is the true oxidant of the olefin[50] and not the peroxy radical as indicated in equation (45).

It is evident that there is still much to be learned concerning ion-catalysed reactions of organic peroxides of all types.

AUTOXIDATION

The essential mechanism of the processes whereby olefins, alkylated aromatic hydrocarbons, aldehydes, ethers and organic compounds of somewhat similar structure are slowly oxidized by air at room temperature and pressure, was clarified about 20 years ago by the structural investigations of FARMER in England and of HOCK and CRIEGEE in Germany. These oxidations are chain reactions initiated in various ways by the generation of active radicals of the types R—O· or R—O—O· that have been mentioned on the preceding pages. HOCK and his colleagues clearly showed that autoxidation proceeds by allylic attack on olefins such as cyclohexene or oct-1-ene with the formation of hydroperoxides[51]

$$\begin{array}{l} \text{—CH—CH=CH—} \\ \quad\;\; | \\ \quad\;\; \text{O—OH} \end{array}$$

while FARMER[52], who independently confirmed this for the esters of unsaturated fatty acids, drew attention to the structural significance of the initial formation of a mesomeric radical

$$\text{A—}\overbrace{\text{CH—CH—CH}}\text{—B}$$

of enhanced stability. The mesomerism of the extended radical, A—(CH—)$_5$—B, of linoleic esters

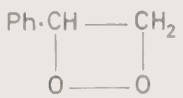
$$CH_3{\cdot}(CH_2)_4{\cdot}CH{:}CH{\cdot}CH_2{\cdot}CH{:}CH{\cdot}(CH_2)_7{\cdot}CO_2R$$

commercially used as drying oils in the paint and linoleum industries, has been well demonstrated by more recent product studies which show (*a*) that though the initial reaction is the homolytic abstraction of a hydrogen atom from the central —CH_2— group of the ester, the oxygen mainly attaches itself to the end of the mesomeric radical, giving a

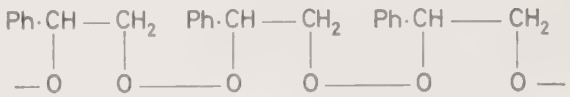
conjugated diene, and (*b*) that *cis-trans* isomerization also occurs during the reaction[53].

Similarly, alkylated aromatic hydrocarbons are always attacked at C—H groups α to the aromatic ring so as to give benzyl radicals, aldehydes yield radicals R—$\dot{C}$=O and ethers, radicals R—$\dot{C}$H—O—R′.

However, a number of olefins which contain no allylic methylene groups, as for example styrene, Ph·CH=CH_2, can be autoxidized. The products from such substances, once thought to be 'moloxides', (IV), are in fact co-polymers of structural type (V)[54]



IV



V

formed by the direct addition of peroxy radicals, R—O—O·, to the carbon atoms of C=C bonds. This addition is particularly favoured by the resonance stability of the benzyl-type radical

$$Ph—\dot{C}H—CH_2—O—O—R$$

formed from styrene and does not so easily occur with simple olefins

$$A—CH_2—CH=CH—CH_2—B$$

for the corresponding radical adduct

$$A—CH_2—\dot{C}H—\underset{\displaystyle O—OR}{\underset{|}{CH}}—CH_2—B$$

is not resonance-stabilized[55]. Nevertheless, the direct attack on double bonds of olefins does occur, concurrently with allylic attack, at elevated temperatures, when homolytic peroxide decompositions rapidly follow and intracticable mixtures of reaction products result.

At low temperatures aldehydes and ethers again yield hydroperoxides. It was from the study of the autoxidation of benzaldehyde to perbenzoic acid that Bäckström[56] in Holland first deduced the sequence of reactions on which all modern kinetic theories of autoxidation are based.

Kinetic Features of Autoxidation

The full reaction sequence for an autoxidation comprises the following reactions

1. $Cat\cdot + R{-}H \xrightarrow{k_1} Cat{-}H + R\cdot$ (initiation)
2. $R\cdot + O_2 \xrightarrow{k_2} R{-}O{-}O\cdot$
3. $R{-}O{-}O\cdot + R{-}H \xrightarrow{k_3} R{-}O{-}O{-}H + R\cdot$ } (reaction chain)
4. $2R\cdot \xrightarrow{k_4}$ Products, e.g. R_2
5. $2RO_2\cdot \xrightarrow{k_5}$ Products, e.g. $R\cdot O_2\cdot R + O_2$ } (chain terminating reactions)
6. $R\cdot + RO_2\cdot \longrightarrow$ Products, e.g. $R\cdot O_2\cdot R$

where R—H is the autoxidizable substrate and Cat is a catalysing free radical.

When the reaction is proceeding steadily, the rate at which new radicals R· are produced by the initiating reaction is equal to that at which radicals R· or $RO_2\cdot$ are destroyed by all the chain-terminating reactions *4* to *6*. Under these conditions the velocity of oxygen uptake by the oxidizing substance R—H is given by the kinetic equation

$$-\frac{\partial[O_2]}{\partial t} = \frac{k_1^{\frac{1}{2}}[Cat]^{\frac{1}{2}}\cdot k_2[O_2]\cdot k_3[RH]}{2\{k_3^2k_4[RH]^2 + k_2k_3k_6[RH]\cdot[O_2] + k_2^2k_5[O_2]^2\}^{\frac{1}{2}}}$$

The autoxidation of many substances has received detailed kinetic study and the results have been accorded frequent review[57]. It has been shown in nearly every instance that k_2 is so much greater than k_3 that, except at very low oxygen pressures, the peroxy radical R—O—O· is dominant in the autoxidizing system, and that chain ending is mainly due to a reaction of type *5*. Thus the rate equation is usually found to be

$$-\frac{\partial[O_2]}{\partial t} = \left\{\frac{k_1}{k_5}\,[Cat\cdot]\right\}^{\frac{1}{2}}\cdot k_3[RH]$$

the first-order dependence on RH indicating that the dominant radical is the one which reacts with the molecule RH (i.e. $RO_2\cdot$), and the square-root dependence on Cat· indicating that chain ending is due to the mutual destruction, by combination or disproportionation, of a pair of radicals.

Organic compounds which are good radical-trapping agents, such as phenols, aromatic amines, quinones, and many natural products, such as flavones found in vegetable oils, can act as 'inhibitors' of autoxidation by removing the active radicals R· or RO_2· so rapidly that one of the main chain reactions, *2* or *3*, is virtually eliminated. If, as is usually the case, the inhibitor removes the dominant RO_2· radical by a process that may be written as

7. $RO_2\cdot + Inh \xrightarrow{k_7}$ Products (unspecified)

then the residual oxidation rate is given by the expression

$$-\frac{\partial[O_2]}{\partial t} = \frac{k_1[Cat\cdot]\cdot k_3[RH]}{k_7[Inh]}$$

but if the R· is the radical removed, it is

$$-\frac{\partial[O_2]}{\partial t} = \frac{k_1[Cat\cdot]\cdot k_2[O_2]}{k_8[Inh]}$$

In each case the inhibited reaction is of first order with respect to the catalyst, since the active radicals are removed one at a time.

The form of the reaction velocity equation thus gives diagnostic information as to the nature of inhibitor action, for it indicates the structure of the radical which initially attacks the inhibitor molecule. For instance, for the autoxidation of benzaldehyde, it has been shown that while phenols react with peroxy radicals, Ph·CO·O_2·, quinones react[58] with benzoyl radicals, Ph·CO·. Product studies, however, show that a whole sequence of reactions can rapidly follow the attack of a radical, RO_2· or R·, on an inhibitor molecule, and in no case is it yet certain that reactions such as *7* have a simple stoicheiometry, as has often been assumed by kinetic investigators.

The Chemical Reactions of Inhibitors (Anti-oxidants)

Inhibitors of any one type, e.g. phenols, can be listed in order of relative efficiency (corresponding to relative values of k_7, the rate constant for the chain-stopping process), but it is now evident that this order is dependent on the structure of the radical RO_2· or, more significantly, on the precise nature of the autoxidizable substrate R—H. For instance, the order of efficiencies of phenols as inhibitors of the autoxidation of

unsaturated vegetable oils is not quite the same as the order for the inhibition of autoxidation of mineral lubricating oils. In general, however, the efficiency of an inhibitor depends on the stability of the radicals which are formed from the inhibitor molecule. For instance amongst phenols which act as reducers of peroxy radicals

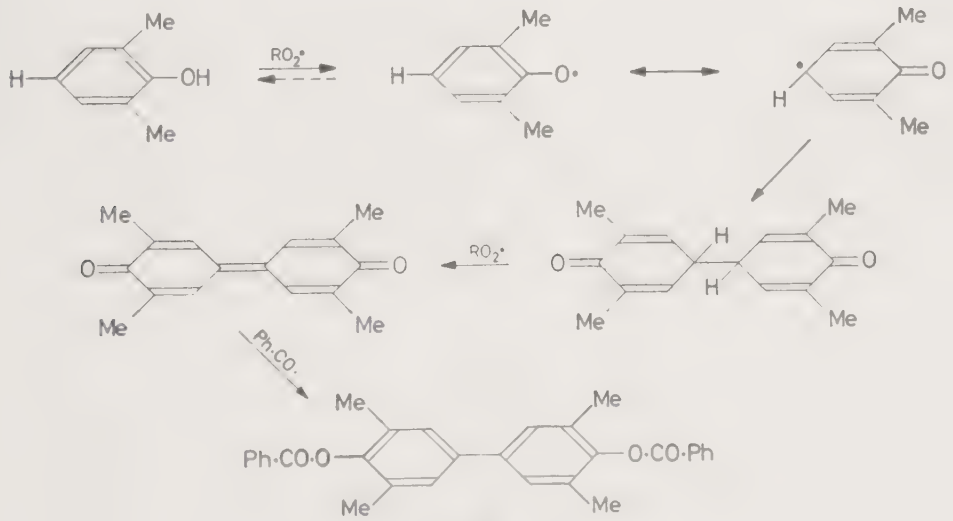
$$(46) \qquad RO_2\cdot + H{-}O{-}Ar \longrightarrow RO_2H + \cdot OAr$$

the most effective inhibitors are the 2:4:6-trialkylated compounds which give mesomeric aryloxy radicals, ·OAr, of sufficiently long free life to be capable of investigation by electron spin resonance spectroscopy. Yet, for technical use, a phenol such as 2:4:6-tri-t-butylphenol which gives the very stable radical (VI) (*cf* p. 39)

VI

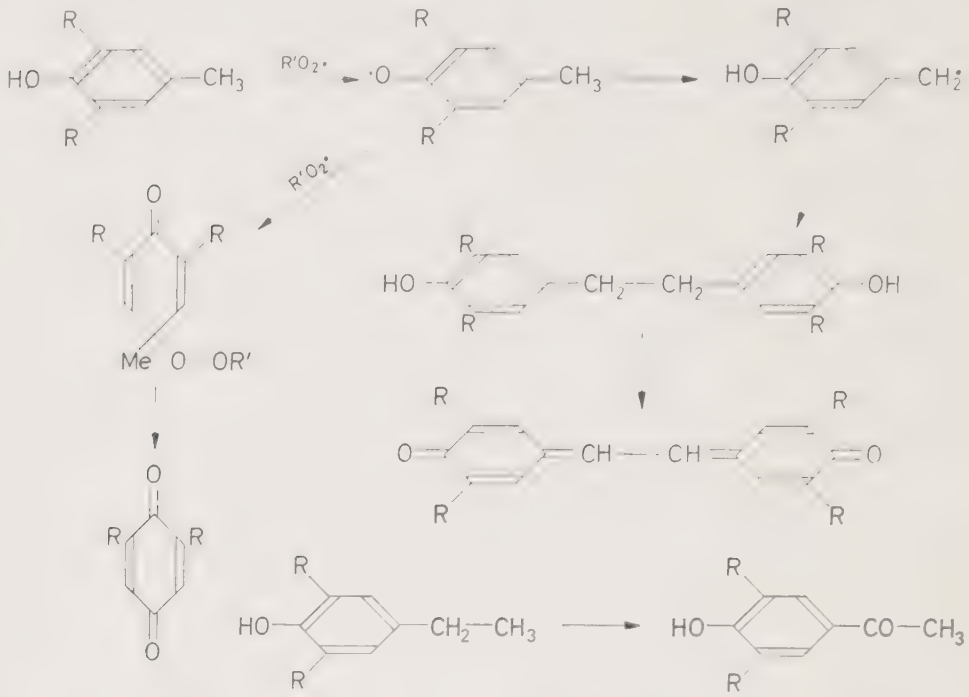
is not as effective as 4-methyl-2:6-di-t-butylphenol from which a whole succession of chain-stopping radicals and molecules can be formed.

The successive reactions of inhibitor molecules with $RO_2\cdot$ and R· radicals vary in type. For instance, 2:6-dimethylphenol retards the autoxidation of benzaldehyde by the following sequence of reactions[58,59]:



21

In the inhibition of the autoxidation of cumene, $Ph{\cdot}CHMe_2$, by trialkylphenols the pattern reaction is different[60,61].

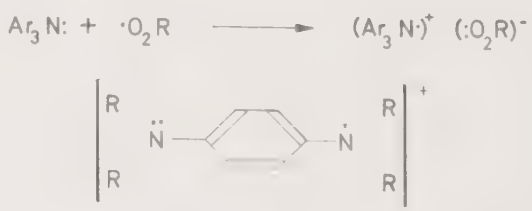


Recent studies (see pp. 38–41) of reactions of free aryloxy radicals are helping to elucidate such reaction sequences.

Primary and secondary aromatic amines are good inhibitors of autoxidation; they may act by yielding stable arylamino radicals, e.g.

$$(47) \qquad Ph_2NH + {\cdot}O_2R \longrightarrow Ph_2N{\cdot} + HO_2R$$

However, tertiary aromatic amines, and in particular *para* di-tertiary diamines, are also excellent inhibitors of the autoxidation of lubricating and transformer oils, and these necessarily must act by electron transfer[36,62], being oxidized, in the first instance, to radical ions, such as those of the Würster's salts (VII).



VII

The intense colour of the eventual oxidation products of such aromatic amines often limits the scope of their technical utility as inhibitors of autoxidation.

The Catalysis of Autoxidation

The nature of the primary catalysts that may initiate the autoxidation of organic compounds is still uncertain, since undetectably small amounts of impurities may suffice. For the autoxidation of purified n-decanal COOPER and MELVILLE[63] have shown kinetically that in the absence of light the rate of reaction is given by the experimental equation

$$-\delta[O_2]/\delta t = k'[R{\cdot}CHO]^{\frac{3}{2}}[O_2]^{\frac{1}{2}}$$

but when irradiated, by the equation

$$-\delta[O_2]/\delta t = k''[R{\cdot}CHO]I^{\frac{1}{2}}$$

I, being the intensity of illumination.
They therefore have inferred that in the dark there must occur, very slowly, direct thermal reaction

(48) $$R{\cdot}CHO + O_2 \longrightarrow R{\cdot}CO{\cdot} + HO_2{\cdot}$$

and, in the presence of radiation that can be absorbed by the aldehyde, the photochemical homolysis

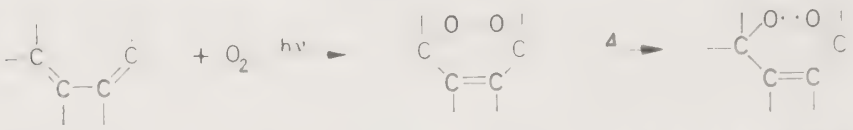
(49) $$R{\cdot}CHO + h\nu \longrightarrow R{\cdot}CO{\cdot} + H{\cdot}$$

The R·CO· radicals in both cases then propagate the oxidation chain by reaction *2* of p. 19, and Cooper and Melville suggest that the radicals $HO_2{\cdot}$ and H· are destroyed on the walls of the reaction vessel. Several other workers have suggested that an electron transfer to oxygen molecules may occur upon the walls of the containing vessel, and this might well be the case with metallic containers or with glass that may contain traces of ions of transition metals such as iron, manganese or cobalt, e.g.

(50) $$Co^{2+} + O_2 \xrightarrow{h\nu} Co^{3+} + (\cdot O{-}O:)^-$$

Again, olefinic compounds can rarely be freed completely from traces of conjugated dienes which, on exposure to light, are prone to combine

with molecular oxygen, yielding cyclic peroxides which, by subsequent thermal decomposition, can form active alkyloxy radicals.



Once active radicals are present, the reactions *2* and *3* of the autoxidation chain produce hydroperoxide molecules, R—O—O—H. Thermal homolysis of the latter then gives R—O· and H—O· radicals, both of which can start fresh reaction chains by the hydrogen abstraction *1*. Consequently, the autoxidations of most reasonably well purified organic molecules at first exhibit *auto-catalysis*, catalyst radicals RO· and HO· being produced more and more abundantly until the thermal rate of hydroperoxide decomposition matches the rate of chain-breaking by the reactions *4* to *6* of p. 19 or *7* (*etc.*) of p. 20.

It has been shown that in olefinic systems the rate of hydroperoxide decomposition, is proportional to $[R—O—OH]^2$, except at very low peroxide concentrations[64]. However, even when present in very low concentrations, ions of transition metals, notably Fe, Co, Mn and Cu (which are used as their oil-soluble salts with the higher fatty acids, such as linoleic and linolenic acids, in paint driers), very markedly promote this peroxide decomposition and consequently are active catalysts of the autoxidation of substances that already contain traces of peroxides. *Figure 1* shows schematically the course of oxidation of a typical unsaturated liquid, (*a*) with no added catalyst, but in which hydroperoxide

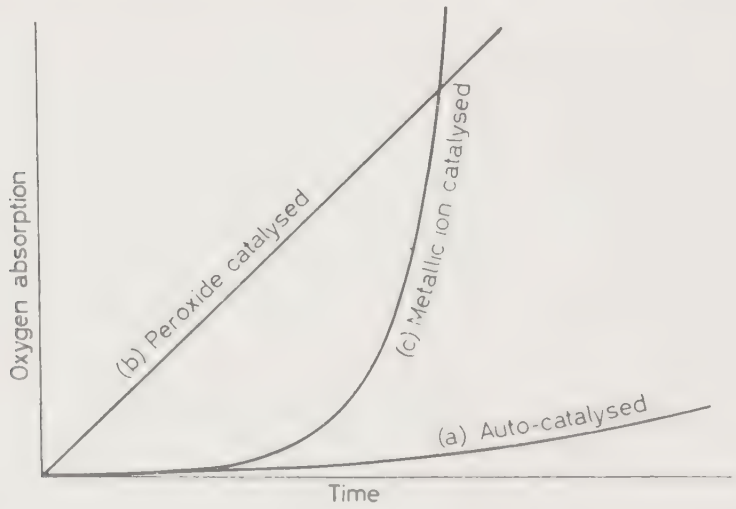


Figure 1

is slowly accumulating, (*b*) with an added peroxide catalyst such as benzoyl peroxide, and (*c*) with the addition of a trace of a salt of a transition metal.

The reactions brought about by these metallic ions resemble chemically the reactions between the same ions and hydrogen peroxide, *viz.*

(18) $R—O—O—H + Co^{2+} \longrightarrow R—O\cdot + Co^{3+} + (:OH)^-$

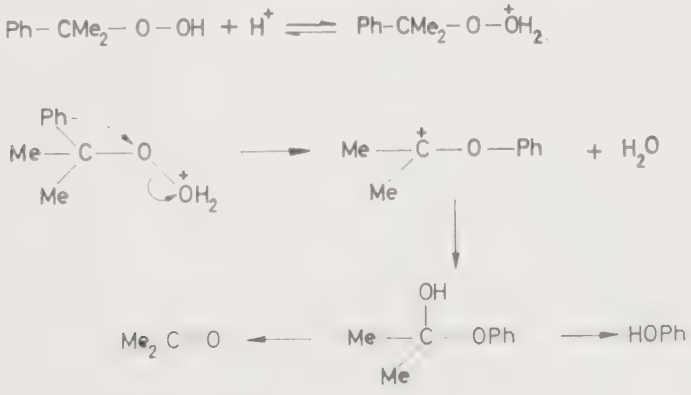
(40) $R—O—O—H + Co^{3+} \longrightarrow R—O—O\cdot + Co^{2+} + H^+$

(42) $R—O—O\cdot + Co^{3+} \longrightarrow R^+ + O_2 + Co^{2+}$

and have already received mention on pp. 15–16.

Both (18) and (40) yield radicals which can catalyse the autoxidation chain reactions given on p. 19: whereas (18) oxidizes the metallic ion, (40) and (42) reduce it again and allow the oxidation-reduction cycle to be repeated, so that a limited amount of metallic ion can catalyse the decomposition of an unlimited amount of hydroperoxide. Eventually a metallic-ion-promoted autoxidation proceeds at a steady rate in which (*a*) the hydroperoxide concentration remains at a low, but constant, value and (*b*) the redox potential of the mixture of metallic ions (i.e. the ratio $[Co^{3+}]/[Co^{2+}]$ for a cobalt-catalysed system) remains constant.

The organic chemistry of reactions (18), (40) and (42) has been worked out in detail for cumyl hydroperoxide, $Ph\cdot CMe_2\cdot O\cdot OH$, by KHARASCH, NUDENBERG and their colleagues[47], and many side-reactions also have been explored. The homolytic reactions listed above bring about the overall reduction $Ph\cdot CMe_2\cdot O\cdot OH \longrightarrow Ph\cdot CMe_2\cdot OH$, but if the mixture becomes acid, then the following heterolytic molecular rearrangement occurs concurrently to give phenol, which then inhibits further autoxidation of the remaining cumene.



This sequence of reactions has been developed in a technical synthesis of phenol from benzene and propylene.

The corresponding reactions for the catalysed decompositions of the hydroperoxides of unsaturated vegetable or animal oils have not been so well elucidated, since such autoxidations yield exceedingly complex mixtures. For instance, R—O· radicals can not only abstract hydrogen atoms from allylic methylene groups, but also they can add to CH=CH bonds, giving more saturated carbon radicals —CH(OR)—$\dot{C}$H— which can polymerize with fresh olefin molecules and also co-polymerize with oxygen (*cf* p. 18). Again, further oxidations of alcohol groups to ketonic groups may occur by reactions indicated below (pp. 33-35), such as the chemical components of dried linseed oil-based paints.

ONE-ELECTRON OXIDATIONS BY IONS CONTAINING TRANSITION METALS

General features

The catalytic role of ions of the transition metals in generating active radicals RO· or R—O—O· from peroxides has been mentioned already. Many compounds of these metals, however, are well known as oxidants that can undergo only a unit valency change, e.g. $FeCl_3$, $K_3Fe(CN)_6$, $[Ag(NH_3)_2]^+$, $Ce(SO_4)_2$. In general the reactivities of these ions follow

Table II. Redox Potentials of some One-Electron Oxidizing Agents

		V
Co^{2+}	$\rightleftharpoons Co^{3+} + e$	+ 1·8
Ce^{3+}	$\rightleftharpoons Ce^{4+} + e$	+ 1·6
Mn^{2+}	$\rightleftharpoons Mn^{3+} + e$	+ 1·5
VO^{2+}	$\rightleftharpoons VO_2^+ + e$	+ 1·1
$Mn(H_3P_2O_7)_2$	$\rightleftharpoons Mn(H_3P_2O_7)_3 + e$	ca. + 1·0
Fe^{2+}	$\rightleftharpoons Fe^{3+} + e$	+ 0·75
$\{Fe(CN)_6\}^{4-}$	$\rightleftharpoons \{Fe(CN)_6\}^{3-} + e$	+ 0·49
$Ag + 2NH_3$	$\rightleftharpoons Ag(NH_3)_2^+ + e$	+ 0·37
Cu^{2+}	$\rightleftharpoons Cu^{2+} + e$	+ 0·17
H^+	$\rightleftharpoons \frac{1}{2} H_2 + e$	0·000
$\{Co(CN)_6\}^{4-}$	$\rightleftharpoons \{Co(CN)_6\}^{3-} + e$	− 0·3
Cr^{2+}	$\rightleftharpoons Cr^{3+} + e$	− 0·42

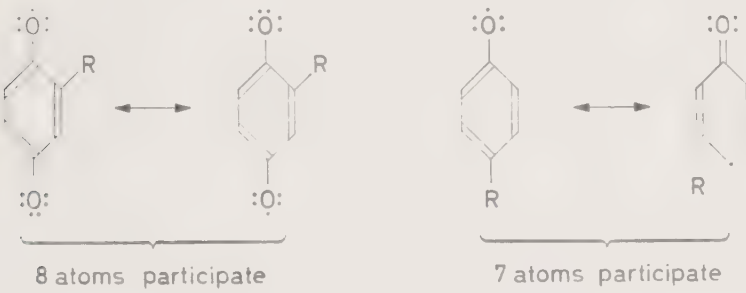
the order of their redox potentials, which are listed in *Table II*, though many details concerning the chemistry of complex ions still need

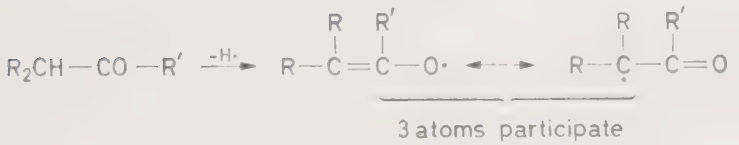
elucidation. At the extremes of this table are ions which may act by generating active radicals from water molecules, e.g.[65, 66]

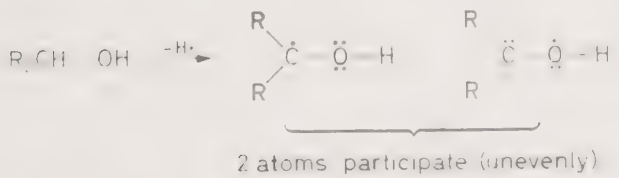
(51) $$Co^{3+} + H_2O \longrightarrow Co^{2+} + H^+ + \cdot OH$$

(52) $$Ti^{2+} + H_2O \longrightarrow Ti^{3+} + (OH)^- + H\cdot$$

and these show little selectivity in their reactions, but in general the oxidizing properties of the reagents of this group are fairly specific and seem to conform to a uniform pattern which can be summarized by the statement that the case of one-electron abstraction from an organic molecule depends on the stability of the free radical formed thereby. Thus the ease of one-electron oxidation of organic molecules is roughly: 1:2- and 1:4-dihydroxy, or diaminobenzenes > monohydric phenols or aromatic amines > aldehydes and ketones (as enols) ≫ alcohols > olefins, but of course it is influenced by the presence of other substituent groups. The following scheme shows how this order can be correlated with resonance stabilization of organic free radicals.







While it is easy to depict the oxidation of the anion of a phenol or an enol as an electron transfer, e.g.

$$(53)\quad (C_6H_5{-}O{:})^- + \{Fe(CN)_6\}^{3-} \rightleftharpoons C_6H_5{-}O\cdot + \{Fe(CN)_6\}^{4-}$$

evidence is now accumulating to show that, in other oxidations effected by metallic ions, the rate-determining process is actually a hydrogen transfer (see the oxidations of alcohols, p. 33). Many inorganic chemists, notably TAUBE[67], now stress the point that the easiest route for electron transfer between two ions may often be through a bridging atom, or group, which moves from association with one metallic centre to another without ever dissociating as a free ion. By following a particular stereochemical course, an atom transfer process may occur by a low-activation-energy path that leads to a highly specific reaction. Few cases of such reactions have yet been studied in detail, but already there are indications that stereo-specific atom transfer processes play a significant role in enzymic oxidations[68].

Many distinctive features of one-electron oxidations of organic molecules can be correlated with the properties of the organic radicals formed thereby. Thus active free radicals, e.g. $R_2\dot{C}{-}OH$ (from oxidations of alcohols or glycols), can initiate vinylic polymerization of olefins[69, 70]

$$(54)\quad R_2\dot{C}{-}OH + CH_2{=}CH{\cdot}X \rightarrow R_2\overset{OH}{\overset{|}{C}}{-}CH_2{-}\dot{C}HX \rightarrow R_2\overset{OH}{\overset{|}{C}}{-}(CH_2{-}CHX)_n{-}CH_2{-}\dot{C}HX$$

while highly stabilized radicals, e.g. $\cdot O{-}C_6H_4{-}OH$, can inhibit such polymerization.

Again, organic free radicals can be both oxidizing and reducing agents[16]

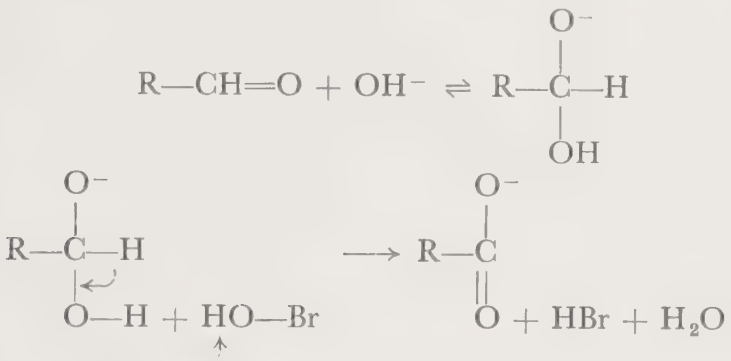
$$(R{:})^- \rightleftharpoons e + R\cdot \rightleftharpoons (R)^+ + e$$

Reactions are known in which a transient radical formed by a one-electron oxidation can effect a reduction. Thus the radical $Me_2\dot{C}{-}OH$, formed by the oxidation of pinacol or of isopropanol, easily reduces mercuric chloride[69, 70]. In contrast, the radical $\cdot CH(CO_2H)_2$ formed by oxidizing malonic acid by Mn^{3+} can, by hydrogen atom transfer, oxidize methanol which is not itself attacked by an organic pyrophosphate[18]. More detailed reviews of one-electron oxidations are given in the following pages.

Oxidation of Aldehydes and Ketones

Text-books of organic chemistry seldom focus attention on the facts (*i*) that ammoniacal silver solutions and Fehling's solution, the characteristic reagents for the detection of aliphatic aldehydes, do not as easily oxidize aromatic aldehydes or (*ii*) that these oxidants do not furnish the corresponding aliphatic acids in good yield. These differences in the behaviour of aliphatic and aromatic aldehydes are not observed with heterolytic oxidants; the latter act by a nucleophilic addition followed by a concerted elimination, e.g.

(55)



in which the hydrogen atom of the —CHO group is removed.

In sharp contrast, the oxidations of the lower aliphatic aldehydes by manganic pyrophosphate are reactions of first order with respect to the aldehyde and dependent on acidity, but they are reactions of zero order with respect to Mn^{3+}, while benzaldehyde, chloral and formaldehyde resist oxidation[71]. These facts indicate that a slow, rate-determining enolization of the aldehyde is followed by a rapid electron abstraction from the enol, or its anion, to yield a mesomeric radical which, in turn, is rapidly oxidized.

(56) $H^+ + R_2CH{\cdot}CH{=}O \underset{\text{fast equilibrium}}{\rightleftharpoons} R_2CH{-}CH{-}OH$

(57) $R_2CH{-}CH{-}OH \underset{\text{slow}}{\longrightarrow} R_2C{=}CH{-}OH + H^+$

(58) $R_2C{=}CH{-}OH \underset{\text{fast}}{\rightleftharpoons} R_2C{=}CH{-}\bar{O} + H^+$

(59) $R_2C{=}CH{-}O^- + Mn^{3+} \rightarrow \underset{\text{VIII}}{R_2C{=}CH{-}O\cdot} \longrightarrow \underset{\text{IX}}{R_2\dot{C}{-}CH{=}O} + Mn^{2+}$

The same features characterize the oxidations of ketones by manganic pyrophosphate[72], though the oxidation step is so much slower that it becomes rate-controlling at low Mn^{3+} concentrations and enolization rate-controlling only at higher Mn^{3+} concentrations. This is illustrated by *Figure 2*.

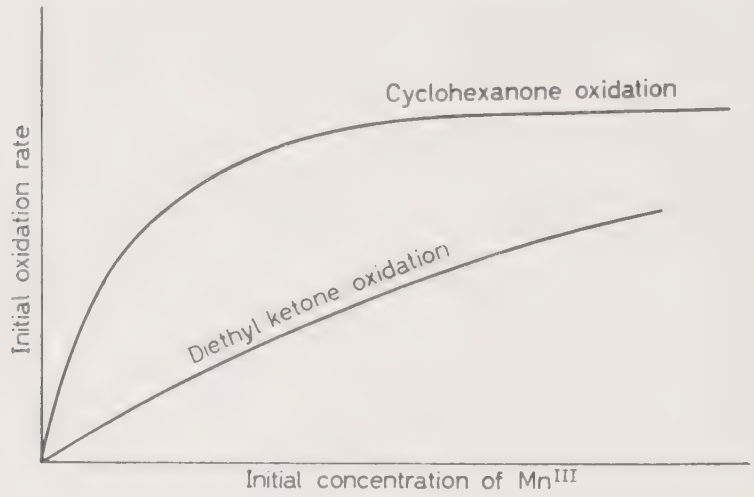


Figure 2

Acid solutions of quinquevalent vanadium[73] and of quadrivalent cerium[74] seem to behave in a similar manner towards both aldehydes and ketones, but since these oxidants can only be used in strongly acid solutions, the oxidation reaction is slower than the enolization and becomes rate-controlling.

The mesomeric radical (VIII or IX), formed by one-electron abstraction from the enol anion of an aliphatic aldehyde or ketone, is a strong reducing agent which is rapidly removed by a fast oxidation

$$(60)\quad R_2\dot{C}{-}CO{-}R' + Mn^{3+} \longrightarrow R_2\overset{+}{C}{-}CO{-}R' + Mn^{2+}$$

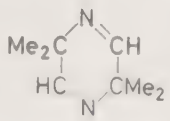
$$(61)\quad R_2\overset{+}{C}{-}CO{-}R' + H_2O \longrightarrow R_2C(OH){-}CO{-}R' + H^+$$

by disproportionation

$$(62)\quad 2R_2\dot{C}{-}CO{-}R' \longrightarrow \begin{matrix} R_2\overset{+}{C}{-}CO{-}R' \\ \downarrow \\ R_2C(OH)CO{-}R' \end{matrix} + \begin{matrix} (R_2\bar{C}{-}CO{-}R')- \\ \downarrow \\ R_2CH{-}CO{-}R' \end{matrix}$$

or perhaps by dimerization. All three routes lead to oxidation at a carbon atom adjacent to the CO group.

From inspection of reaction velocities DRUMMOND and WATERS[72] favour reaction (62) for cyclohexanone oxidation by inorganic pyrophosphate from which they were able to isolate α-hydroxycyclohexanone. Again from the oxidation of isobutanal, $Me_2CH{-}CHO$, by the free radical $\cdot ON(SO_3K)_2$, ALLEN and WATERS[75] obtained evidence for the formation of the hydroxy, aldehyde, $Me_2C(OH)\cdot CHO$, while from hot ferricyanide oxidation of this aldehyde CONANT and ASTON[76] obtained a good yield of the pyrazine (X): but, at that time, they



X

rejected an oxidation mechanism involving enolization on the grounds that potassium ferricyanide does not oxidize olefins.

Oxidations of aldehydes, ketones and nitroparaffins by alkaline ferricyanide, however, do seem to follow enolization, since their reaction velocities are usually proportional to the product

$$[\text{Organic substrate}] \times [OH^-]$$

though the reaction order with respect to [Ferricyanide] depends on the compound being oxidized, as is to be expected if enolization velocities (equation 57) and one-electron oxidations (*cf* equation 59) are of comparable order.

Ketones and nitroparaffins both need enolization by caustic soda solutions at *p*H 12–14 before they are oxidized at a comparable rate to aldehydes in carbonate buffers at the lower *p*H range of 9–11. This more facile enolization of aldehydes than of ketones may, in part, explain the distinctive actions of ammoniacal silver hydroxide and of Fehling's solution upon aldehydes, but the reactions of the latter reagent have some peculiar features. For instance, the oxidations of glucose and of acetoin evidently require the prior formation of an anion of the ene-diol

$$R\cdot CO{-}CH(OH)R' \xrightarrow{OH^-} R{-}\overset{O^-}{C}{=}\overset{OH}{C}{-}R'$$

for the oxidations to 1:2-diketones, $R\cdot CO\cdot CO\cdot R'$, do not attain their maximum velocity until some cuprous ions are present in the solution[78].

Acraldehyde, $CH_2{=}CH{-}CH{=}O$, and crotonaldehyde, $CH_3{-}CH{=}CH{-}CH{=}O$, which cannot form enols of normal type, are easily oxidized in acid solution, in which they can form mesomeric cations. Thus acraldehyde

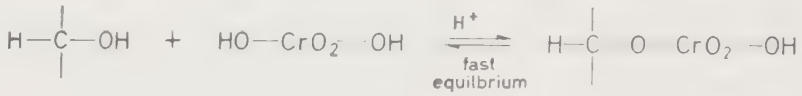
$$(63)\quad CH_2{=}CH{-}CH{=}O + H^+ \rightleftharpoons CH_2{=}CH{-}\overset{+}{C}H{-}OH \longleftrightarrow \overset{+}{C}H_2{-}CH{=}CH{-}OH$$

$$(64)\quad \overset{+}{C}H_2{-}CH{=}CH{-}OH + H_2O \rightarrow HO{-}CH_2{-}CH{=}CH{-}OH$$

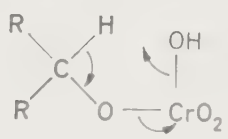
gives the enol of β-hydroxypropionaldehyde which can oxidize to glyceraldehyde, $HO{-}CH_2{-}CH(OH){-}CH{=}O$, and evidently reacts subsequently as a 1:2 glycol[79].

Oxidation of Alcohols and Glycols

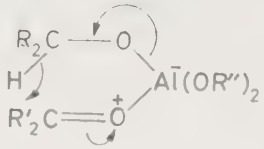
The normal routes for the oxidation of primary and secondary alcohols involve a concerted heterolytic elimination which often follows a reversible esterification. With the oxidations that have received detailed study it has been shown that the C—H bond of the carbinol group is severed in the rate-determining step[80], e.g.



Though in some oxidations (e.g. heterolytic decomposition of alkyl hydroperoxides[81]) this elimination of H^+ requires the presence of a base catalyst, in others the oxidant may itself be able to supply the proton-accepting group by forming a cyclic reaction complex, e.g. (XI)



XI



XII

The latter is structurally similar to the complex involved in the Meerwein Pondorff–Oppenauer reaction, which is usually viewed as a hydride-anion transfer, i.e. (XII). However, the directions of electron

movements in cyclic transition complexes such as (XI) and (XII) are indeterminate and could almost as well be written in the reverse manner.

Homolytic oxidation of alcohols again involves, in most molecules, the C—H bonds of the carbinol group. As indicated already (p.14), many active radicals such as Ph·, Me·, Cl·, $Me_3C—O·$, Ph·CO·O· and $Cl_3C·$, can attack these C—H bonds directly, and often reaction chains can be set up.

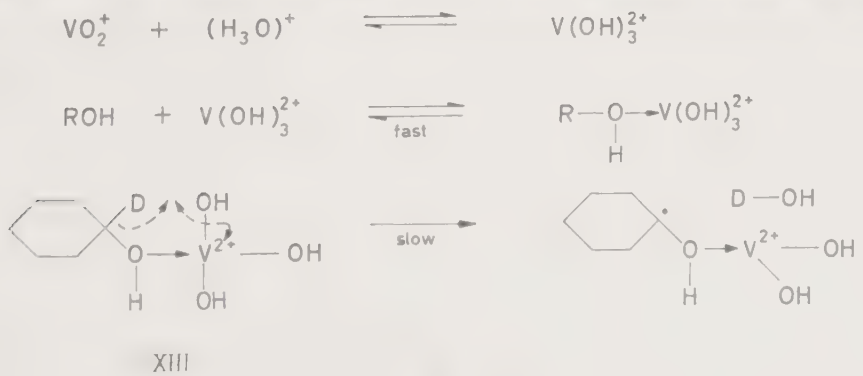
One-electron abstracting agents attack primary and secondary alcohols only with difficulty. BAWN and WHITE have suggested that the very reactive Co^{3+} ion attacks methanol at the O—H groups[82], i.e.

(65) $CH_3—O—H + Co^{3+} \longrightarrow CH_3—O· + H^+ + Co^{2+}$

(66) $CH_3—O· + Co^{3+} \longrightarrow CH_2=O + H^+ + Co^{2+}$ *fast*

and similar suggestions have been made concerning the oxidations of hydrated formaldehyde $H_2C(OH)_2$ by both Co^{3+} and Ce^{4+} ions[83, 84] in strongly acid solutions

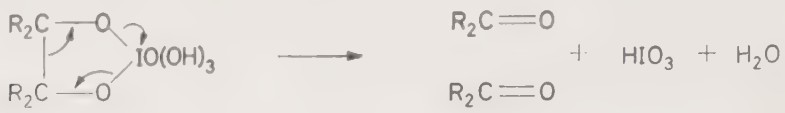
More recent work of LITTLER and WATERS who have compared the rates of oxidation of cyclohexanol and 1-deuterocyclohexanol, indicates that the fission of C—H bonds can be involved in the rate-determining step of oxidations of alcohols by metallic ions, for both with ceric sulphate[85] and with acid quinquivalent vanadium they have found that the deuterated alcohol oxidizes more slowly than ordinary cyclohexanol. In the oxidation of cyclohexanol in perchloric acid solution it was found that the yellow cation $\{V(OH_3\}^{2+}$ responsible for the oxidation reacted immediately with the alcohol to give a red complex, which then decomposed slowly to yield a blue solution of a vanadyl salt (V^{IV}) and transient organic radicals, $R_2\dot{C}—OH$, that could initiate the polymerization of acrylonitrile, giving a polymer that contained hydroxyl groups[86]. The oxidation of the alcohol must therefore occur in stages



XIII

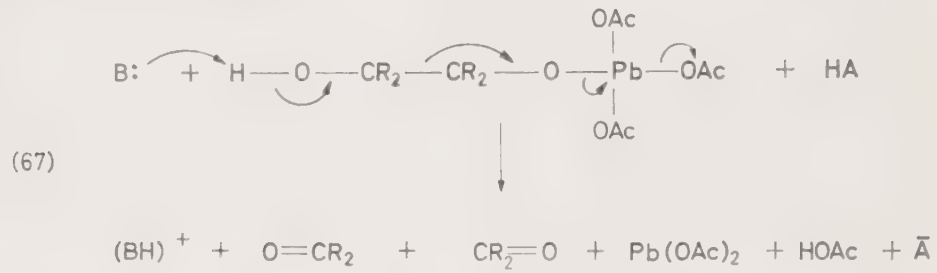
and the C—H must be severed homolytically in the red complex by an electron redistribution which is analogous to those which occur heterolytically in the complexes (XI) and (XII). In all these cases the oxidation proceeds by a specific low-activation-energy path.

Though simple tertiary alcohols are most difficult to oxidize, pinacol, $HO{\cdot}CMe_2{-}CMe_2{\cdot}OH$, is easily cleaved to acetone by both one-electron and two-electron removing agents. There is now strong evidence that heterolytic oxidants of the latter group, and in particular lead tetra-acetate and periodic acid[87], oxidize 1:2-glycols by forming complexes in which electron movements such as those shown in (XIV)



XIV

probably occur, but cyclic acid or base-catalysed reactions such as (67) cannot be excluded[88].



(67)

The cyclic heterolytic glycol fissions have their homolytic equivalents, for Drummond and Waters[69] have given kinetic evidence to indicate that the oxidation of pinacol by manganic pyrophosphate is preceded by the reversible formation of a complex (XV) which slowly decomposes to acetone and a $Me_2\dot{C}$—OH radical, detectable by the polymerization of acrylonitrile and by its ability to reduce mercuric chloride.

XV

Vanadium^{V} and Ce^{IV} also oxidize pinacol to acetone in this way[70,89] but, unlike the ring-forming heterolytic oxidants, the one-electron-abstracting agents seem to attack secondary 1:2-diols, such as ethylene

and propylene glycols, or the isomeric cyclohexane-1:2-diols as if they were simple alcohols; i.e. they effect the oxidation :CH(OH) $\longrightarrow$:C=O and, in this respect, resemble chromic acid[90].

For Ce^{IV} and V^{V}, steric considerations probably favour the formation of complexes such as (XIII), in which C—H bonds are broken, rather than complexes such as XV, in which C—C bonds are broken, but these are clearly not the same for all oxidizing agents[90, 91]. However, both chromic acid and acid V^{V} solutions do oxidize pinacol monomethyl ether under conditions in which tertiary butanol cannot be oxidized[91, 92]. In this case the essential structural feature may be the resonance stability of the resultant free radical

$$Me_2\dot{C}—\ddot{\underset{\cdot\cdot}{O}}—Me \longleftrightarrow Me_2\ddot{C}—\dot{\underset{\cdot\cdot}{O}}—Me$$

for several monohydric alcohols which cannot give chelate complexes, e.g. β-phenylethanol and phenyl-t-butylmethanol, undergo extensive C—C bond fission when oxidized with V^{V} or chromic acid[93, 94].

$$PhCH_2{\cdot}CH_2{\cdot}OH + V^{V} \longrightarrow Ph{\cdot}CH_2{\cdot} + CH_2O + V^{IV}$$
$$\longrightarrow PhCHO + HCO_2H$$

$$PhCH(OH)CMe_3 + V^{V} \longrightarrow PhCHO$$
and not $Ph{\cdot}CO{\cdot}CMe_3$

Here the reaction paths of least activation energy are evidently decided by the resonance stability of radicals such as $Ph{\cdot}CH_2{\cdot}$ and of molecules such as PhCH=O. Similarly, oxidations of α-hydroxy acids with both Mn^{III} and V^{V} take the path[95, 96].

$$R—CH(OH)—CO—OH \longrightarrow R—\dot{C}H(OH) + CO_2$$

These acids may form chelate ring complexes with the oxidant but, in addition, the resonance stability both of CO_2 and of radicals $R{\cdot}\dot{C}H{\cdot}OH$ can favour C—C fission.

Oxidation of Phenols

(a) Quinols—The electrochemical oxidation of 1:4-dihydroxybenzenes to 1:4-benzoquinones is a reversible process with a *p*H-dependent

redox potential that is dependent on the nature of any substituent groups present, but potentiometric equilibrium is not established immediately.

Electrophilic groups (NO_2, CN, CO_2H, Halogens) raise the redox potential, making the quinone a better oxidizing agent[97]. From certain highly substituted quinones, such as duroquinone, the corresponding semi-quinone radical-ions (XVI) can be formed in alkaline solution

XVI

and their physical and magnetic properties can be studied[98]. In acid solution the semi-quinone radical ions are unstable but nevertheless they do take part in the oxidation–reduction reactions of quinones. Thus, though ferric ions can completely oxidize quinols (QH_2), the rate of this oxidation is retarded by the presence of ferrous ions, so that the first two following reactions[99] are measurably slow (·QH indicates the semi-quinone radical)

$$\text{(68)} \qquad Fe^{3+} + QH_2 \underset{k_2}{\overset{k_1}{\rightleftharpoons}} Fe^{2+} + \cdot QH + H^+$$

$$\text{(69)} \qquad Fe^{3+} + \cdot QH \xrightarrow{k_3} Fe^{2+} + Q + H^+$$

but $$\text{(70)} \qquad Fe^{2+} + H^+ + Q \xrightarrow{k_4} Fe^{3+} + \cdot QH$$

can rapidly proceed to completion.

Quinones can be used effectively as dehydrogenators of organic molecules, but the question as to whether they act as homolytic, or only as heterolytic, oxidants is still a moot point, for cyclic reaction mechanisms can often be assigned to their reactions[100]. Undoubtedly quinols can be dehydrogenated by free radicals[101], whilst quinones easily pick up free radicals at their oxygen atoms[59,102].

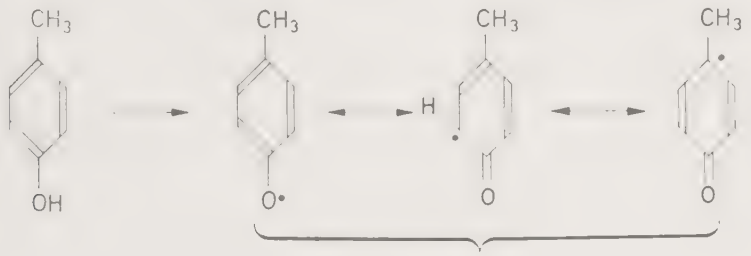
(*b*) *Monohydric phenols*—In many cases these can be oxidized by one-electron-abstracting agents. In 1930, Fieser[103], following earlier work by Conant[104] on the oxidation of *ortho* and *para* diphenols and diamines, found that there appeared to be a linear relation between the percentage of oxidation of a phenol in a given time and the initial redox potential of the oxidant, and computed for many phenols 'critical oxidation potentials' at which no oxidation was discernable in five

minutes. He suggested that, for phenol oxidations by one-electron removal, fast equilibria such as

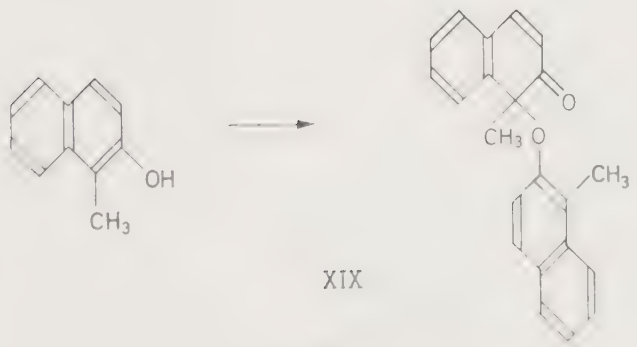
$$(53) \qquad (ArO)^- + \{Fe(CN)_6\}^{3-} \rightleftharpoons ArO\cdot + \{Fe(CN)_6\}^{4-}$$

were followed by slow irreversible reactions in which ArO· radicals were destroyed by dimerization or by further oxidation. Later kinetic measurements[105] show the inadequacy of this theory and demonstrate that a ' critical oxidation potential ' gives no more than a qualitative description of the oxidizability of a phenol.

The oxidation of phenols by alkaline ferricyanide was first studied by PUMMERER[106] who isolated many dimeric products $(ArO\cdot)_2$ in which aromatic rings had been united by C—C coupling in *ortho* or *para* positions to the original OH groups, (XVII), or by coupling through oxygen (e.g. XVIII, XIX). Typical examples are

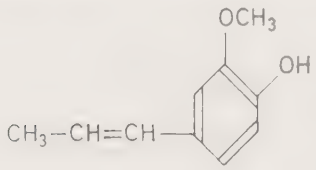


XVII XVIII

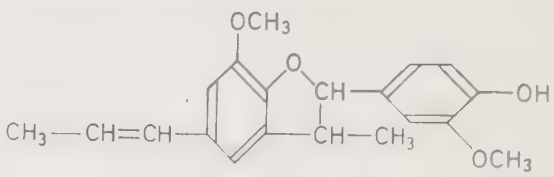


XIX

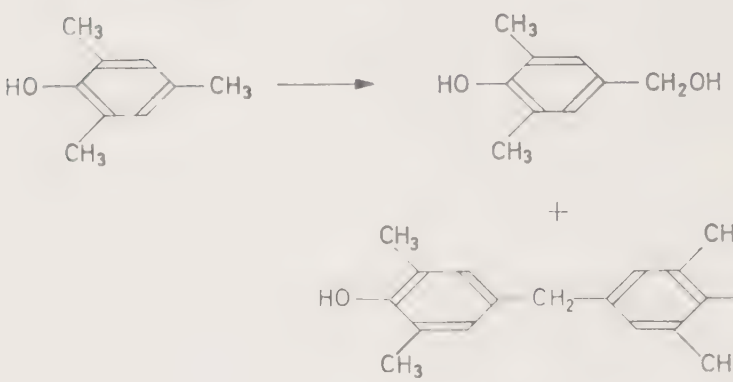
Of particular interest amongst these is the formation from *p*-cresol of 'Pummerer's ketone', the correct formula of which (XVIII) was finally established by Barton, Deflorin and Edwards[107]. A similar range of dimeric products has been obtained by oxidizing phenols electrolytically[108], by ferric chloride, by Fenton's reagent[109] or by a persulphate together with a trace of a silver salt[110]. Many workers have commented on the significance of these oxidations in connection with the biogenesis of complex aromatic plant products, including alkaloids: with phenols related to lignin, coupling through conjugated



*iso*Eugenol



XX



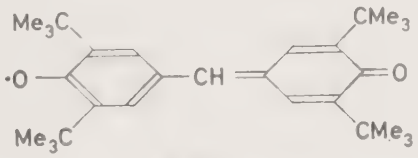
XXI

side-chains can also occur[111], e.g. (XX), and sometimes alkyl substituents can be lost in the oxidation. Thus the oxidation of 2:4:6-trimethylphenol[109, 110] gives the diphenylmethane (XXI) amongst other products. Amorphous polymers containing some ether linkages often constitute the main products of chemical oxidation of phenols[105, 110] and, perhaps for this reason, laboratory attempts to verify biochemically plausible syntheses of natural products have, with a few notable exceptions[107], frequently been unsuccessful.

In the last decade a significant advance in the understanding of mechanisms of phenol oxidation has come from parallel series of investigations by Cook and his collaborators in the U.S.A.[112] and by Müller and Ley[113] in Germany. These workers independently showed that 2,4,6-tri-t-butoxy phenol could be oxidized by alkaline

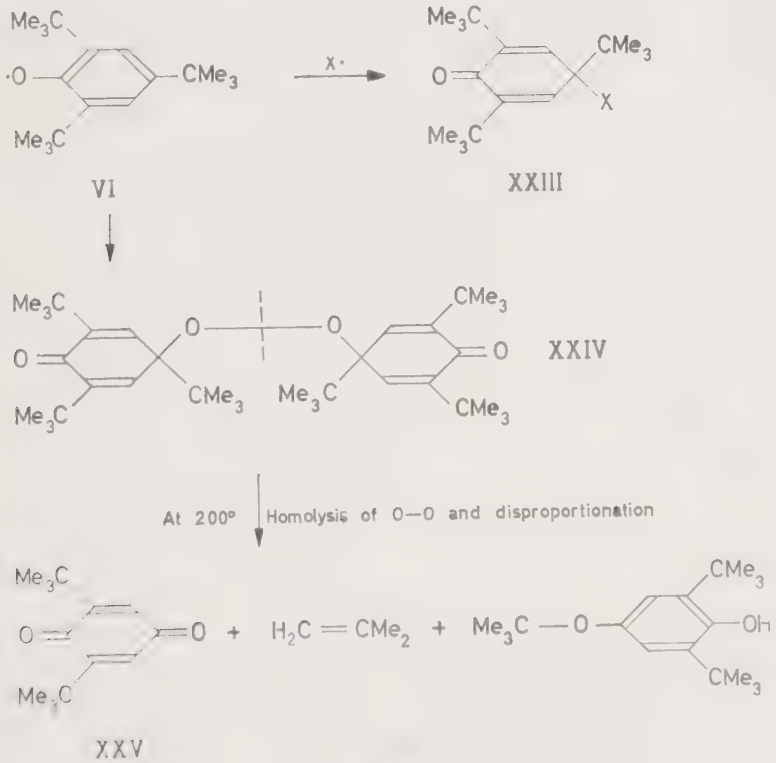
ferricyanide, or by a suspension of lead peroxide, to a blue solution containing the free radical (as VI, see p. 21) which can be studied spectroscopically and magnetically so that the spatial distribution of the unpaired electron can be investigated[114].

Blue or red solutions of this type have now been prepared from several other phenols in which all *ortho* and *para* positions to the OH have been substituted by groups which do not bear a hydrogen atom at an α-position to the benzene ring[115], e.g. tertiary alkyl, alkyloxy or phenyl[116]. The most stable free aryloxy radical yet prepared[117] is (XXII).



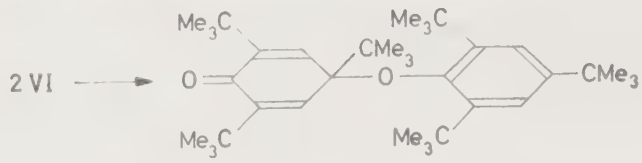
XXII

These free aryloxy radicals immediately react with halogens or nitrogen dioxide to give quinonoid adducts of structures (XXIII) (X=Br or NO_2), and with oxygen to give peroxides (XXIV) that decompose thermally as shown below[118].



The quinone (XXV) can also be obtained directly from the phenol by the use of an excess of ferricyanide.

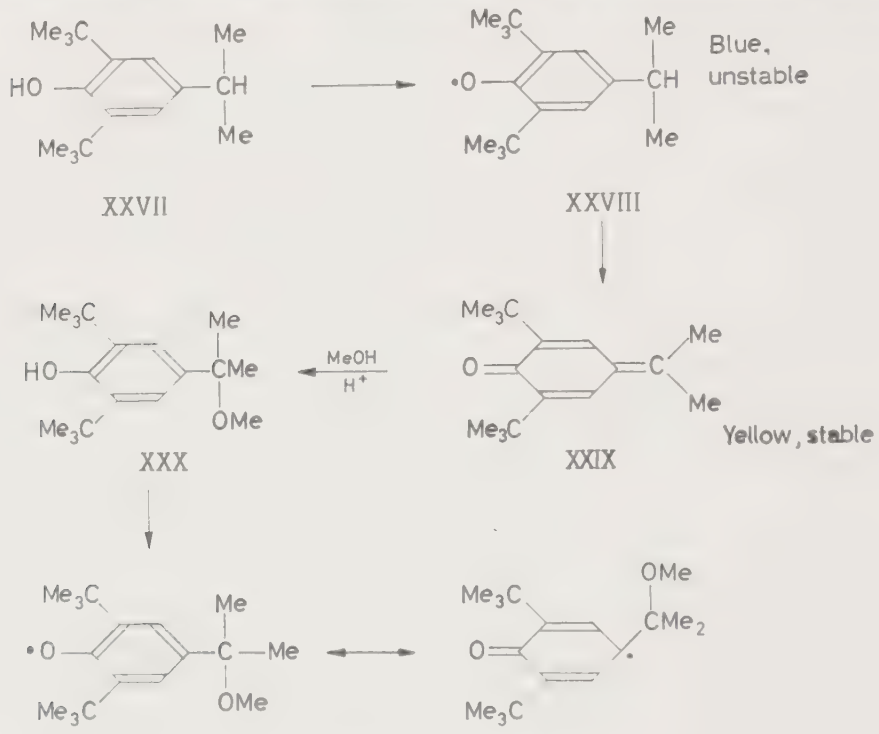
Most of the radicals themselves decompose slowly to disproportionation products and may yield diamagnetic dimers (XXVI) which have been synthesized[119] from compounds of type (XXIII).



XXVI

The free aryloxy radicals can be used to oxidize reversibly other phenols that yield less stable radicals[119, 120].

An interesting case of ferricyanide oxidation is afforded by the phenol (XXVII) which gives a deep blue radical (XXVIII) that soon disproportionates, by a second-order reaction, to the original phenol (XXVII) and the yellow quinone–methide (XXIX). The latter can be converted by the action of methanol, in the presence of a trace of acid, to a phenol (XXX) which can be oxidized[121] to a stable radical (XXXI).



No definite radical formation has been observed with either 2:6-di-t-butylphenol or 4-methyl-2:6-di-t-butylphenol, both of which are oxidized by several one-electron-abstracting reagents to dimeric products and quinones, by routes that have been indicated from autoxidation studies (pp. 21 and 22)[115,120].

The succession of reactions which these aryloxy radicals can undergo may today conveniently be studied by means of paramagnetic electron spin resonance[122], for the fine structure of the electron resonance spectrum of a free radical can have a pattern distinctive enough for both mathematical analysis and diagnostic use. Since the homolytic oxidation of phenols is of technical importance in connection with their uses as anti-oxidants (see pp. 20–22), this subject is now receiving intensive study, for when small percentages of aromatic compounds are added to commercially important substances, and in particular to edible fats and oils, it is important to know whether they might eventually break down to undesirable coloured or possibly toxic, oxidation products.

Much of the older experimental work needs re-evaluation, for already the discovery that free aryloxy radicals combine directly with oxygen has shown that little reliance can be given to studies of phenol oxidation that have been carried out in solutions exposed to the air.

Many aspects of the homolytic oxidation of organic compounds are thus matters of considerable present interest, and so it may well be that the subject matter of this chapter may need substantial revision in a few years' time.

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2

DEVELOPMENTS IN HYDROXYLATION OF PHENOLS

James D. Loudon

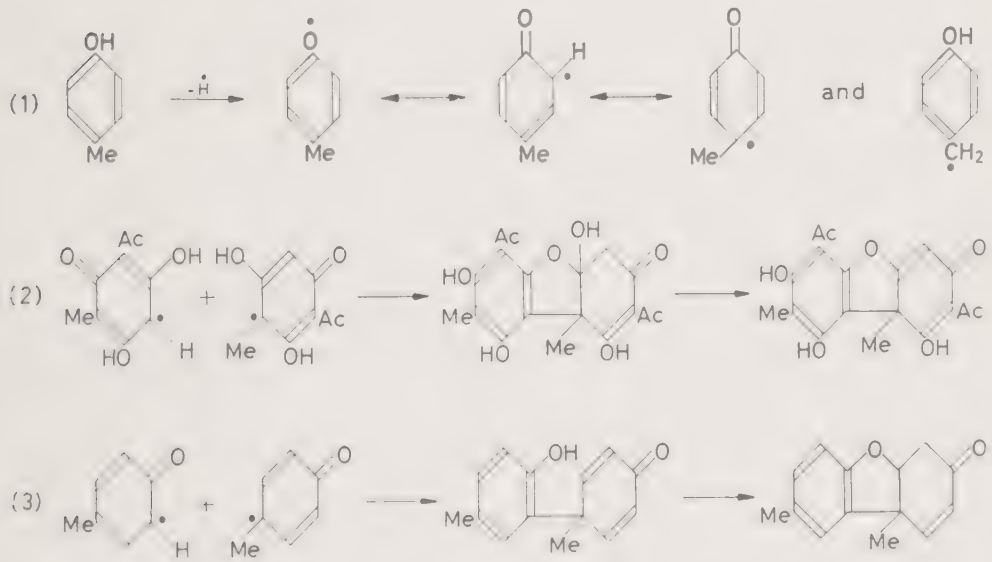
The hydroxylation of phenols may be considered to include any process, whether direct or indirect, whereby a hydroxyl group replaces a hydrogen atom of the phenol system. Such a definition covers a large area of chemistry and of biochemistry, because both in nature and in the laboratory the result is achieved in many ways, not all of them clearly understood. Enzymatic hydroxylation of phenols is a particular aspect of their biological oxidation, a subject which attracts deservedly widespread attention and inquiry[1]. Hydroxylation is one of the methods[2] used in the animal organism to dispose of phenol and phenol derivatives, and indeed of aromatic compounds generally, which are foreign to normal metabolism. Recent work points to variety and specialist functions in the natural agents responsible. Thus it is known that liver microsomes[3] have an enzyme system which is capable of hydroxylating foreign aromatic compounds but is inert towards normal substrates such as tryptophan and phenylalanine: yet these also can be hydroxylated in the animal body. Hydroxylation of the *ortho*- or *para*-centres in a phenol ring is as potulate of hypotheses[4,5] which attempt to trace the biogenesis of natural products, and this in itself indicates the importance of the operation as an item of chemical practice. In attempts to elucidate or imitate natural processes of hydroxylation numerous chemical models have been designed. Their

study merges with others, less specifically conceived, on the mechanism of hydroxylation as it applies to aromatic compounds and to phenols in particular. All of these contribute to the accumulated store of information upon which the organic chemist draws for the preparation or synthesis of polyhydric phenols.

This chapter is primarily concerned with preparative methods. It is not exhaustive either of the number of methods available or of the use made of any particular one. It deals with topics mostly of recent origin and still in course of development. In that sense it is a progress report.

SUBSTITUTION BY FREE RADICALS

Although in some respects an over-simplification, a qualitative picture (1) of phenol oxidation as initiated by reagent free radicals can be formed on the assumption that the phenol (illustrated by *p*-cresol) is first dehydrogenated to a mesomeric radical which may then dimerize in one of several possible ways or combine with reagent radicals. Where an alkyl side-chain is present in the phenol, radical intermediates of the benzyl type sometimes participate in the reactions.



It frequently happens that dimerization and combination with reagent radicals compete with each other, and the prevailing course may then depend very largely on the reaction environment. Oxidative phenol coupling is beautifully illustrated by BARTON's synthesis[6], *cf.* [2], of

usnic acid from *C*-methylphloracetophenone: this is modelled on the simple oxidative dimerization (3) of *p*-cresol and is effected by potassium ferricyanide (*cf* p. 38). It may be regarded as the culmination of a longheld belief that biogenetically such processes are of far reaching consequence, and this theme has been developed by BARTON and COHEN[7]. Combination of phenolic and reagent radicals has results no less important, if less spectacular (see also p. 21).

Hydroxyl Radicals

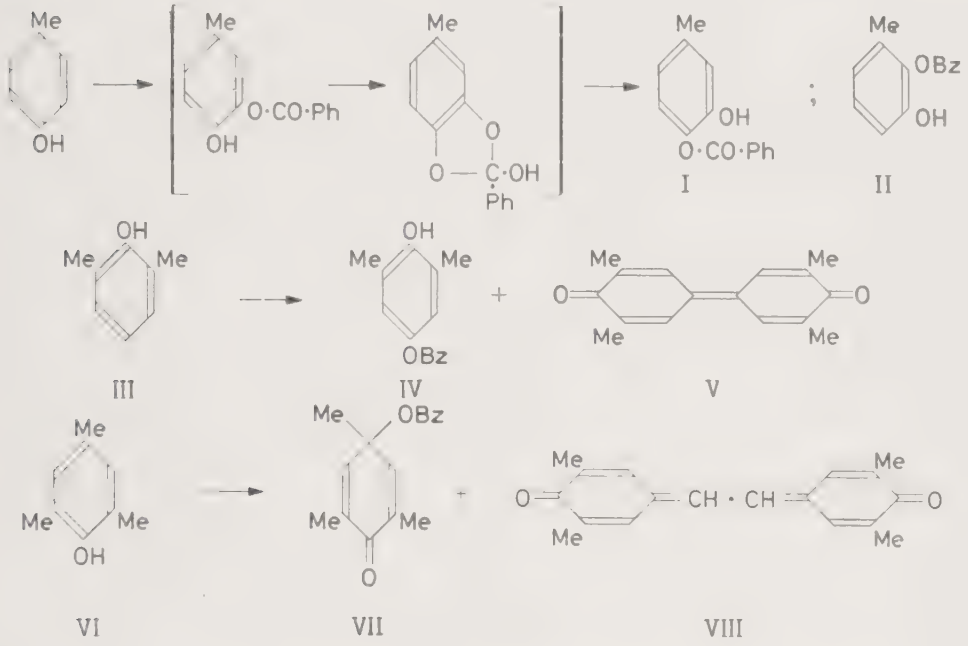
Fenton's reagent—hydrogen peroxide in presence of ferrous sulphate—was regarded by WIELAND[8] as a model for oxidation by heavy-metal enzyme systems and is a well authenticated source of free hydroxyl radicals. It hydroxylates phenols to catechols and hydroquinones, but the process is seriously complicated by side-reactions[9, 10]. These are greatly reduced when the hydroxyl radicals are generated through the action of penetrating radiation on water. From phenol[11], by the use of X-rays on aqueous solutions in presence of oxygen, the hydroquinone–catechol ratio in the products is between 1·5 and 2 in neutral solution, rising to between 4·0 and 4·7 in acidic or alkaline media; resorcinol is not found, but the formation of quinonoid products occurs towards the extremes of the *p*H range. This exclusive *o*:*p*-hydroxylation holds for phenols generally and contrasts with hydroxylation of chlorobenzene[12], nitrobenzene[10] or benzoic acid[13], each of which under similar conditions yields all three possible isomers. Broadly, the same contrast is found in the monohydroxylated metabolites formed when aromatic compounds are administered to animals, but the parallelism is incomplete and can hardly justify the inference that enzyme-generated hydroxyl radicals are responsible.

Tyrosine is oxidized to 3:4-dihydroxyphenylalanine by exposure in aqueous solution to ultraviolet radiation[14]. Phenol, in common with other aromatic compounds, is destructively oxidized under the influence of ultrasonic radiation[15].

Acyloxy Radicals

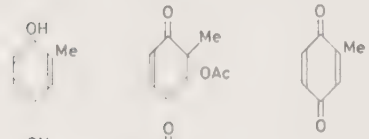
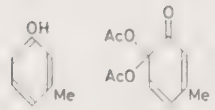
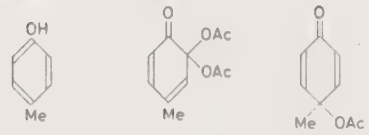
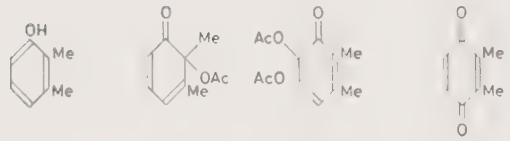
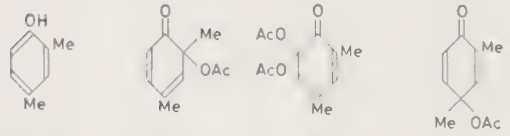
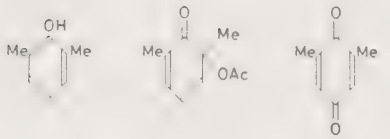
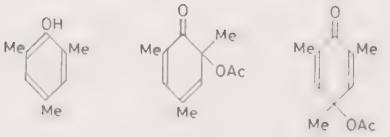
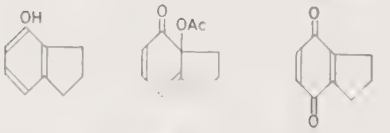
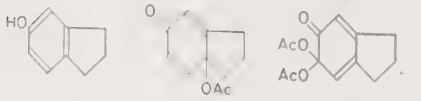
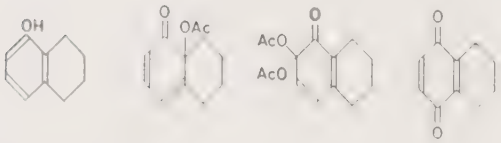
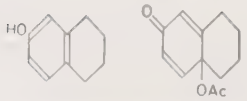
From the preparative point of view there are greater potentialities in the attack of acyloxy radicals upon phenol homologues although phenol itself yields mainly resinous products. In chloroform, benzoyl peroxide reacts[16] with *p*-cresol affording 4-benzoyloxy-3-hydroxytoluene (I; yield, 35 per cent): with *m*-cresol it gives the same product in poorer yield (20 per cent) and with *o*-cresol gives traces of the benzoate (II)

together with much tar. There is evidence that radicals derived from the solvent may also take part in such reactions[17] (*cf* p. 14). The structures assigned to the benzoates (I) and (II) are based[16] on unequivocal syntheses of the methyl ethers formed from them by reaction with diazomethane, and it is therefore clear that introduction of the benzoyloxy group is sometimes accompanied by migration of benzoyl to a preferred site on another oxygen atom. A plausible course of rearrangement[18] is illustrated for the case of *p*-cresol, although the ease of migration in the weakly polar environment is remarkable.



Benzoyl peroxide reacts in a similar way with *m*-4- and *m*-5-xylenols, and with the monomethyl ethers of hydroquinone or resorcinol it likewise yields 2-benzoyloxy-5-methoxyphenol. Cosgrove and Waters[19] consider that there is a strong tendency for the benzoyloxy group to enter a position adjacent to the phenolic hydroxyl, and this is supported by the results obtained with *m*-2-xylenol (III) where the benzoate (IV) is formed only in minor amount (10 per cent) and the main product is the diphenoquinone (V; yield, 50 per cent) together with the corresponding dihydroxydiphenyl (10 per cent). On the other hand, from mesitol (VI) the dienone (VII) predominates (90 per cent yield) and is accompanied by traces of the stilbenequinone (VIII).

Table I

Phenol	*Products*	*Reference*
		23
		22,23
		23
		22,24,25
		26
		22,24,27
		24
		22
		26
		26
		26,28
		25,29

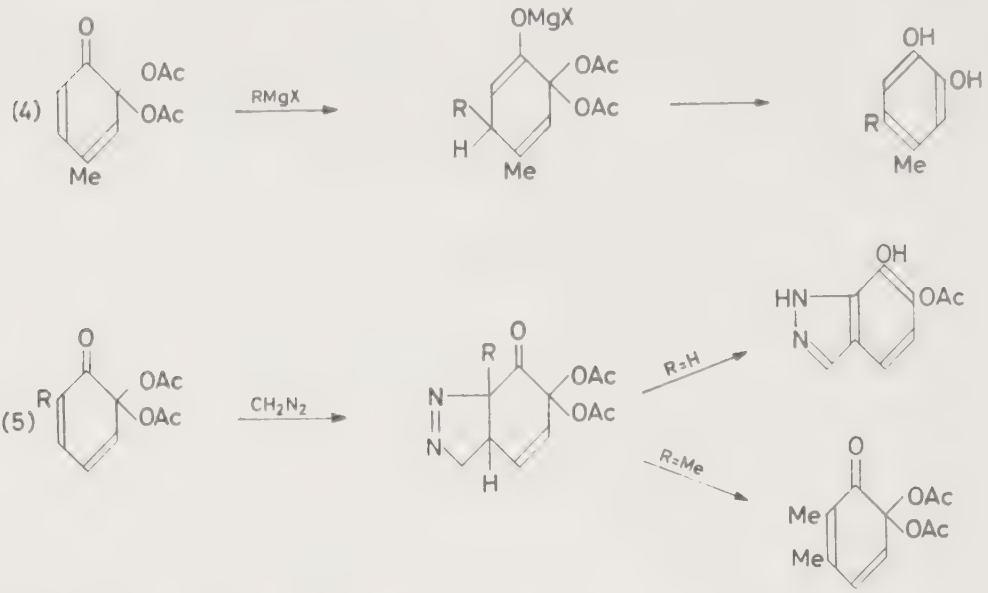
A survey by Wessely and Schinzel[20] shows greater variety in the products formed in acetic acid from acetyl peroxide in reactions with the isomeric cresols and 2:4-dimethylphenol. Thus, after saponification, dihydric phenols are obtained corresponding to entry of the hydroxyl group into free *para*- as well as free *ortho*-positions and, in addition, derivatives of *o*-hydroxyphenylacetic acid are found, indicating that the radical, $\cdot CH_2CO_2H$, participates in the reactions[17].

Wessely Acetoxylation

Far reaching potentialities, still not fully exploited, are contained in products kindred in type to the dienone (VII) and formed by *C*-acetoxylation of phenols in acetic acid by lead tetra-acetate. This last must surely rank as one of the most versatile of chemical reagents[21], and included in its repertoire is the ability to furnish acetoxyl radicals. Wessely and his colleagues[22,23] have shown that the nature and extent of its reactions with phenols depend on the number of free or alkylated (*o*:*p*-)positions therein. The simpler phenols are again extensively resinified, but the products isolated or detected in a representative number of cases are listed in *Table I*, with the major product formulated first. The acetoxylated cyclohexadienones are classified on the basis of their quinonoid structures as acetates or *gem*-diacetates of the so-called *o*- or *p*-(alkyl- or hydroxy-)quinols. Individually they are identified by analysis, by the crossed or continuous conjugation revealed in the ultraviolet spectrum and by hydrogenolysis which uniformly replaces one acetoxyl group and yields, according to type, the original phenol or a derived catechol monoacetate. In the latter case, where the catechol nucleus is unsymmetrically substituted, transesterification (or acetyl migration) intervenes to form a mixture of the two isomeric monoacetates. This can be hydrolysed directly to the homogeneous catechol, and a practicable route is thereby opened from 4-alkylphenols to 4-alkylcatechols.

4:5-Disubstituted catechols may be prepared (reaction 4) through initial 1:4-addition of organometallic reagents to such *gem*-diacetates as the one obtained from *p*-cresol[30]. Moreover, diazomethane adds to the double bond which is adjacent to the ketonic group of a *gem*-diacetate, affording pyrazolines as adducts[31]. These undergo thermal decomposition, the process yielding a derivative of 6:7-dihydroxyindazole

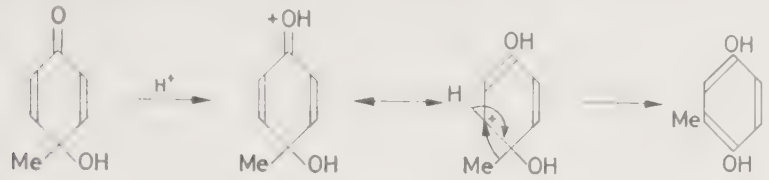
preferentially or a methyl homologue of the *gem*-diacetate where aromatization is blocked (reaction 5).



Dienone–phenol Rearrangements

It is the special merit of Wessely acetoxylation that, in spite of mixed products and moderate yields, it makes accessible *o*- and *p*-quinols already known in part[32] and patently fertile for synthesis. Many of their reactions are beyond the scope of this chapter: others, especially those involving aromatization through molecular rearrangement, lead to dihydric phenols in some variety. Although mild alkaline hydrolysis or base-catalysed methanolysis may liberate a *p*-quinol from its acetate[29, 33], both of these, as illustrated for *p*-toluquinol, are subject to rearrangement[25] in either aqueous acid (6) or aqueous alkali (7). Thereby a hydroquinone derivative is formed by migration of the alkyl group, a result which recalls the formation of methylhydroquinone, *via* *p*-toluquinol, when *p*-cresol is oxidized by potassium persulphate in acid solution[34]. On the other hand, an acetoxyl group migrates and a derivative of resorcinol is formed (8) when the *p*-quinol or its acetate is exposed to the conditions of Thiele acetylation (acetic anhydride in presence of concentrated sulphuric acid), and a similar change—to a resorcinol monoacetate—is induced in the *p*-quinol acetate by ethereal boron trifluoride[25]. This dualism of rearrangement is also influenced by the substituents in the *p*-quinol[25], and a variant is shown[35] in reaction (9).

(6)



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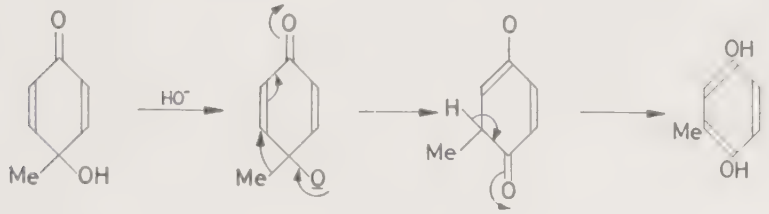

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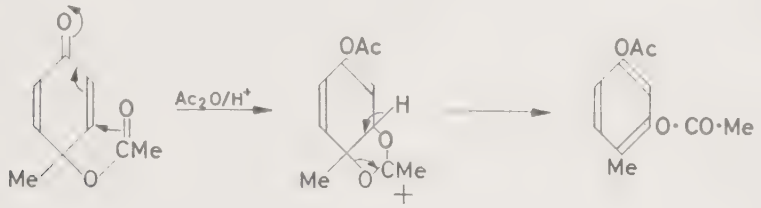

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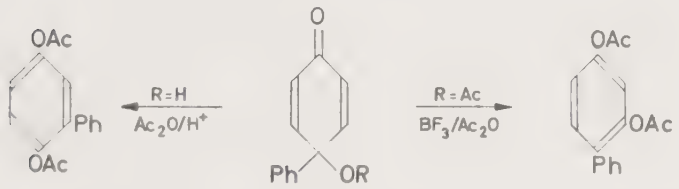
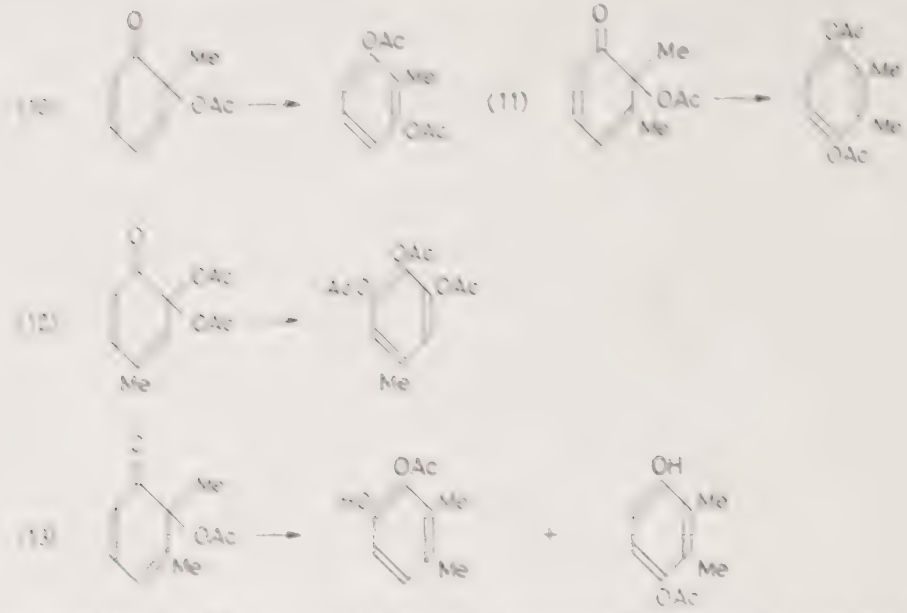
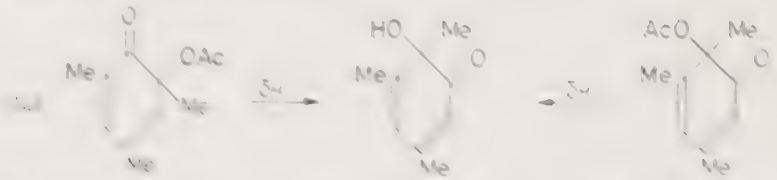


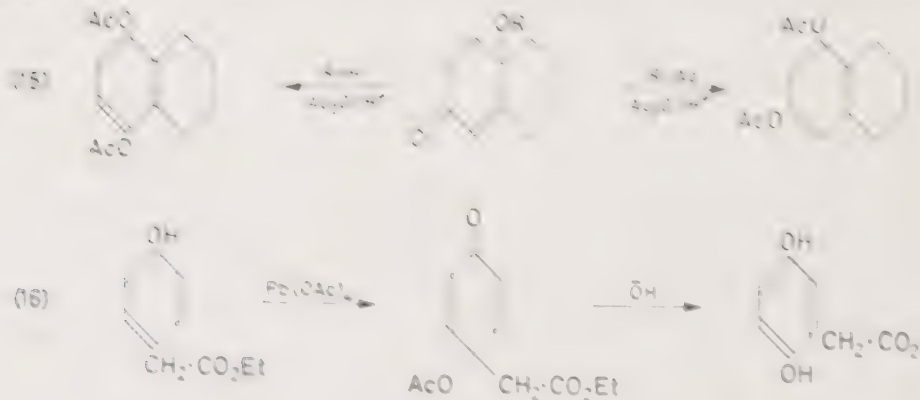
Boron trifluoride and the Thiele reagent likewise cause rearrangement of *o*-quinol acetates which afford, respectively, mono- and *di-acetates* of 2-substituted resorcinols (reaction 10), but alternatively, where this preferred course is blocked, form derivatives of hydroquinone[27] (reaction 11). Still another orientation of product is found in the pyrogallol derivative which is obtained[25] under Thiele conditions from the *gem*-diacetate of 2-hydroxy-4-methyl-*o*-quinol (reaction 12). In contrast with the ring-contraction (to 2-acylcyclopent-3-enones) suffered by free *o*-quinols[36] at 450°, both *o*- and *p*-quinol acetates are aromatized at this temperature, migration of acetoxyl—sometimes complicated by transesterification (reaction 13)—leading to mixed monoacetates of catechols and hydroquinones[36]. It should also be noted that *o*-quinols which are substituted in the 6-position are subject[37] to a rearrangement of the acyloin type (reviewed[38]) which favours formation of the 3-substituted isomer



(reaction 14) and is incurred during attempts to liberate the 6-substituted quinol from its acetate.

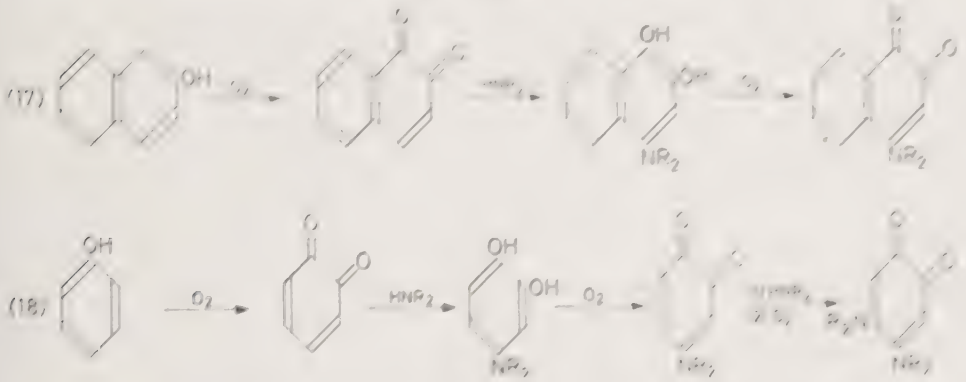


These dienone–phenol rearrangements are more fully discussed from the mechanistic viewpoint by WITKOP[23] and by WESSELY[35]. Their extension to dicyclic compounds (*cf* reactions 15)[25, 39] and to related steroids[39, 58] derived from estrone and estradiol-17β emphasize their practical value. They may also be significant biologically[24, 40]; thus the reactions (16), now realized in practice, might well be analogous to the final stages in the biological oxidation of tyrosine to homogentisic acid.



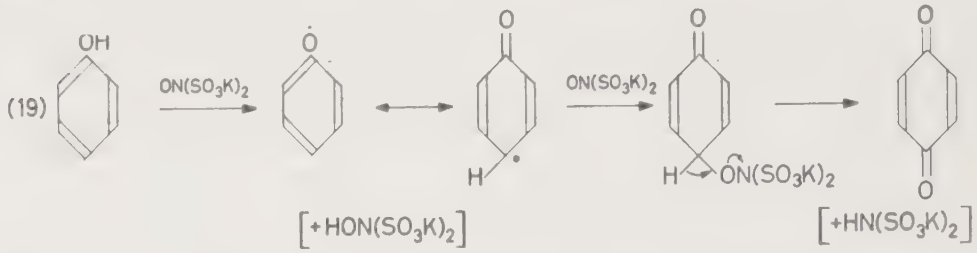
OXIDATION TO QUINONES

Quinones are common byproducts of controlled oxidation of phenols. *p*-Benzoquinones, readily accessible[41] through oxidation of phenols, anilines or their *p*-amino-derivatives, can become sources of hydroquinones whereas, until recently, *o*-benzoquinones were generally prepared in the laboratory from preformed catechols. In this context it is interesting to note the marked extent to which *ortho*- competes with *para*-oxidation in examples to be found in the preceding section. It is also noteworthy that BRACKMAN and HAVINGA[42], in search of a homogeneous catalytic system to simulate the action of tyrosinase, find that copper amine complexes catalyse the oxidation of monohydric phenols by molecular oxygen to derivatives of amino-*o*-quinone. The reactions which proceed smoothly at room temperature yielding products free from *p*-quinones, are considered to involve direct oxidation of the phenol to an *o*-quinone, followed by addition of the amine employed and further oxidation of the resultant aminated catechol. Thus, with morpholine (HNR_2) as the amine, 2-naphthol yields 4-morpholino-1:2-naphthaquinone (reaction 17) whereas phenol affords 4:5-dimorpholino-1:2-benzoquinone (reaction 18). Cupric acetate also oxidizes aniline in methanol, yielding the monoanil of 2-amino-5-anilino-1:4-benzoquinone as the main product[43].

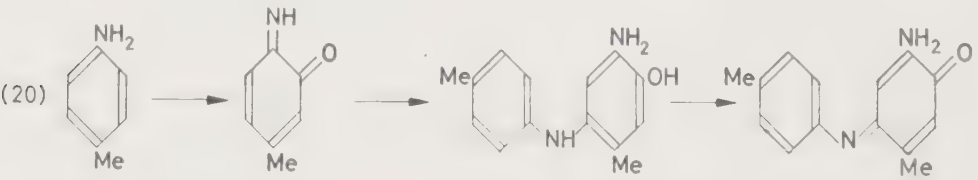


Frémy's salt—potassium nitrosyldisulphonate, $ON(SO_3K)_2$— has come to be recognized as one of the most efficient agents for oxidizing monohydric phenols to *o*- or *p*-quinones[44]. The salt[45]—an unstable, deep-yellow, solid dimer—is completely dissociated in water, forming a purple solution which is tolerably stable in the pH range, 8–11, and contains the ion radical, $ON(SO_3^-)_2$. This, in reaction with a phenol (course 19), first abstracts a hydrogen atom and then combines with the resultant phenolic radical to form an intermediate which can be

isolated in particular cases[46] but usually decomposes rapidly into the quinone and potassium imido-sulphate. In this behaviour of the intermediate lies the essential difference between the reaction and the Elbs persulphate oxidation where, in a similarly constituted intermediate, prototropic change, instead of elimination, leads to a derivative of hydroquinone.



The process is notable for its generally good yields and for the quality of its products. It is particularly valuable for oxidizing *p*-substituted phenols to corresponding *o*-quinones[47], although *para*-oxidation prevails in absence of the blocking (*p*-) substituent. By its use quinones have been prepared from various naphthol derivatives[48] including equilenin[49]. Frémy's salt also oxidizes[50, 51] aniline and its homologues to quinoneimines which, however, react further with the aniline, so that the end-product of the reaction is an aminoquinoneanil (*cf* reaction 20). Derivatives of nitrosobenzene are byproducts of these oxidations[50], and 2-nitrosomesitylene is the main product[51] from mesidine wherein all of the *o*:*p*-positions are substituted. Diphenylamine is oxidized to *p*-benzoquinoneanil[52].

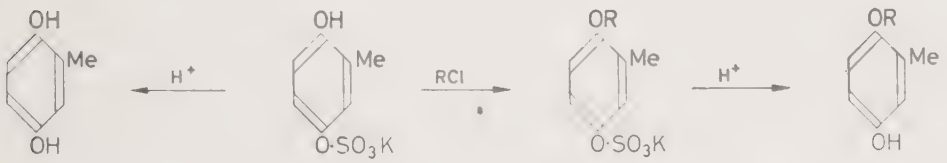


ELBS (PERSULPHATE) AND DAKIN OXIDATIONS

These two reactions may be considered briefly together, less because of any inherent similarity than because they are both well known and have long been paired as alternative processes for hydroxylating phenols. Both owe much of their development to the work of BAKER and his colleagues[53].

Elbs persulphate oxidation consists in treating a phenol in aqueous alkaline solution (the addition of solvent pyridine is sometimes advantageous) with ammonium or potassium persulphate, whereby an

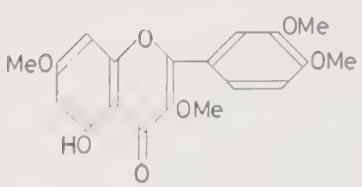
hydroxyaryl sulphate, e.g. (IX) is initially formed and affords the dihydric phenol upon acid hydrolysis. The substituting agent in the reaction appears to be[53] the sulphate ion radical, $\dot{O}SO_3^{\ominus}$, and the practicable process is that of *para*-hydroxylation, although catechols are found as byproducts[54] and can be prepared, but only in low yield, from *p*-substituted phenols. In this way Elbs[55] obtained nitrohydroquinone (30–40 per cent yield) from *o*-nitrophenol. Subsequent applications of the method—up to the year 1947 and including its use in the synthesis of naturally occurring derivatives of tetra-[56] and penta-[57] hydroxybenzenes—are summarized by Baker and Brown[53] who also adapt it to the preparation of hydroquinone monoalkyl ethers by alkylating the intermediate sulphate prior to hydrolysis. Both monoalkyl ethers of an unsymmetrically substituted hydroquinone can be prepared—the one (X; R = alkyl) by the route just described, the other *via* the benzyl ether (X; R = CH_2Ph) similarly obtained and then successively alkylated and de-benzylated.



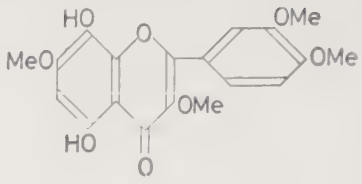
IX X

Seshadri[5] has reviewed the extensive and fruitful use of the reaction (and of the Dakin reaction) which he and his school have made in the synthesis of natural products. Many of his syntheses follow possible biogenetic paths: for instance the flavanol, gossypetin (XII; H for each Me), is synthesized[58] from its congener, quercetin (XI; H for each Me), *via* their respective tetramethyl ethers, (XI)→(XII). Again, in the depside field, an example of preferential nuclear oxidation is furnished by hydroxylation of methyl haematommate to methyl 5-hydroxyhaematommate (reaction 21) which is related to the *meta*-didepside, thamnolic acid[59].

Apart, however, from its synthetical use hydroxylation can be an aid to controlled degradation of a complex phenol, and the principle is neatly illustrated from xanthone chemistry. Here, among naturally occurring members, a 1- (or 8-)hydroxy-substituent is commonly present and, in a given case, the free or substituted state of the nuclear position which is *para* to the hydroxyl group can be ascertained by the



XI

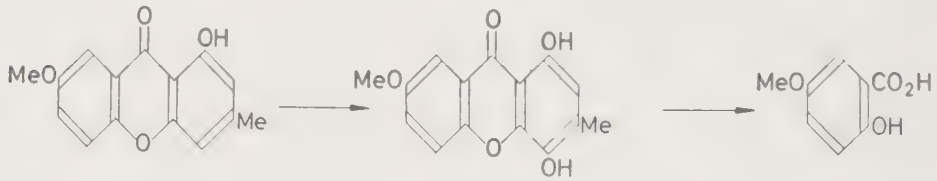


XII

(21)

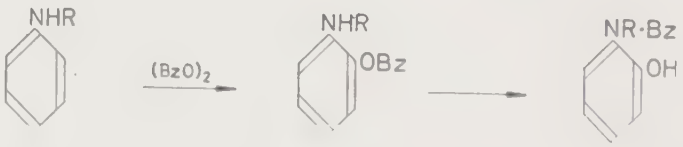
colour reaction[60] (Gibbs test) with 2,6-dichlorobenzoquinone chloroimide. When this position is free, hydroxylation by the Elbs method, followed by further oxidation with hydrogen peroxide in alkali, leads to a derivative of salicylic acid (reaction 22) and, hence, establishes most of the substitution pattern in the phenol[61].

(22)



Anilines differ from phenols in undergoing predominantly *ortho*-substitution by reaction with persulphate in alkali[62]. This leads, *via* *o*-aminophenyl sulphate esters, to *o*-aminophenols, anthranilic acid for instance yielding 3-hydroxyanthranilic acid[63], although it may be noted that *o*-aminobenzaldehyde yields *o*-aminophenol[64]. Benzoyl peroxide similarly converts *N*-alkylanilines into *o*-benzamidophenols (reaction 23)[65]. Perhaps eventually it will be possible so to control such hydroxylations that they yield *ortho*- or *para*-derivatives at will.

(23)

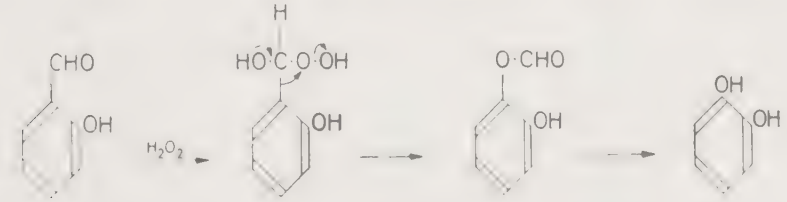


Hydrogen peroxide in alkali oxidizes *o*- and *p*-hydroxy-benzaldehydes or -acetophenones to catechols and hydroquinones, respectively. Dakin[66] regarded his reaction as being applicable mainly to aldehydes

but its extension to ketones by BAKER[67] has been amply confirmed. Since, in general, hydroxyacetophenones are more accessible than hydroxybenzaldehydes, this extension adds greatly to the practical value of the process. In so far as it leads to derivatives of catechol, the Dakin reaction is the complement of the Elbs reaction and as such finds its principal use. Practical difficulties which arise from the tendency of *ortho*-acylated phenols to form sparingly soluble, probably co-ordinated sodium or potassium salts are avoidable[68] by using tetramethylammonium or benzyltrimethylammonium hydroxide instead of alkali.

Under Dakin conditions, phenols are not usually formed from arylaldehydes which lack an *o*- or *p*-hydroxyl group, but it is possible that the role of this group is facilitating rather than fundamental to the course of the reaction, *cf* (24). Thus hydrogen peroxide in ether, which scarcely affects benzaldehyde, oxidizes 2,4-dimethoxy- and 2,4,5-trimethoxybenzaldehydes to corresponding methoxyphenols[69]. Moreover, salicylaldehyde is almost quantitatively converted into catechol[70] by hydrogen peroxide at 100° and into catechol monoformate[71] by peracetic acid in acetic anhydride at 25°. These reactions, however, are more closely identified with the acid-catalysed Baeyer-Villiger oxidation (reviewed by HASSALL[72]) whereby ketones and aldehydes are converted into esters, R·CO·R′ → R·CO·OR′, in reaction with hydrogen peroxide or with peracids, of which peroxytrifluoroacetic acid[73] is the most effective. For this type of oxidation it is established that the migratory aptitude of an aryl group is proportional to its capacity for electron release[74], and this in turn has a bearing on the reactions to be discussed in the following section.

(24)



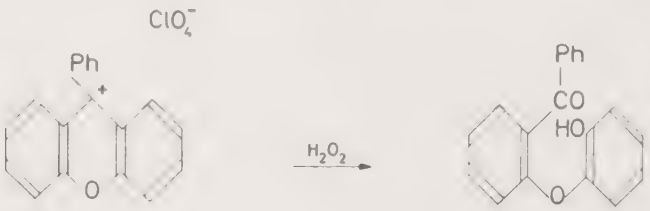
It will be appreciated that *ortho*-hydroxylation of a phenol as effected through the Dakin reaction is dependent on preliminary *ortho*-acylation of the phenol by one or other of the standard methods. These methods—the Fries[75], Gattermann[76], Hoesch[77] and Reimer-Tiemann[78] reactions have been reviewed—are not, however, exclusively *ortho*-substituting.

ORTHO-HYDROXYLATION

To achieve hydroxylation which is specifically *ortho* in a phenol, it seems almost imperative to anchor some reagent through the phenolic oxygen atom and so to choose the reagent that it is sterically and chemically fitted to react further with the *ortho*-position. If this second step is not in itself an hydroxylation, then it must be designed to provide a product which is conducive to hydroxylation.

Catechol Derivatives

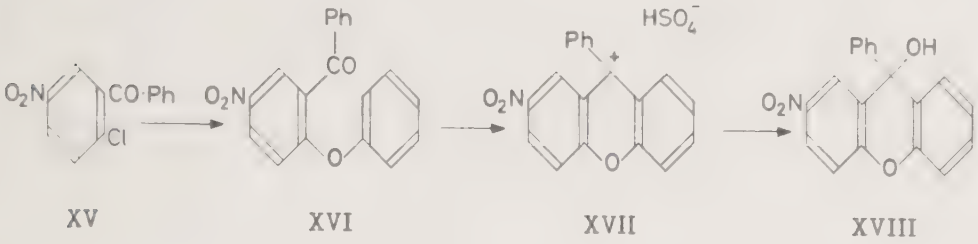
Developing this scheme Loudon and his colleagues[79] adopted as prototype a reaction described by Quint and Dilthey[80] who showed that 9-phenylxanthylium perchlorate (XIII) is oxidized by hydrogen peroxide in acetic acid to 2-(2′-hydroxyphenoxy)benzophenone (XIV). The perchlorate is obtained from 9-phenylxanth-hydrol which in turn



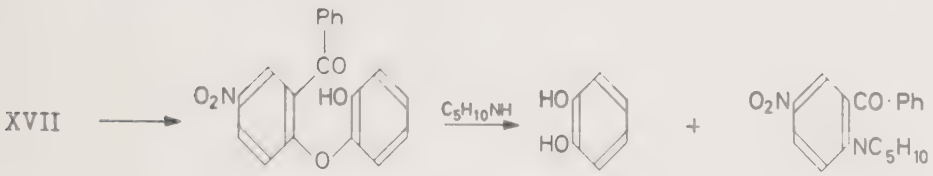
XIII XIV

is prepared from xanthone and phenylmagnesium bromide, but although xanthone derivatives are moderately accessible this type of synthesis is limited. However, for the purpose in mind a more compact, and at the same time more flexible, synthesis[81] of 9-phenylxanthylium salts is found in condensing 2-chloro-5-nitrobenzophenone (XV) with the sodium salt of a phenol, followed by dissolving the resultant ether, e.g. (XVI), in cold concentrated sulphuric acid which causes rapid cyclization to the xanthylium sulphate, e.g. (XVII). The sulphate need not be isolated. The red solution in sulphuric acid, so prepared, affords the corresponding xanth-hydrol (XVIII) when poured into water, but it can be used directly, when diluted with acetic acid, for oxidation by hydrogen peroxide. Thereby a very convenient route is opened to catechol intermediates of type (XIX). In order to liberate the dihydric phenol from this intermediate, the latter is warmed with piperidine which displaces the hydroxylated aryloxy group yielding an easily separable mixture of the catechol (XX) and 5-nitro-2-piperidino-benzophenone (XXI)[79,82]. This method of splitting diaryl ethers which

carry an *o*- or *p*-nitro group is well known from work by LE FÈVRE and TURNER[83].



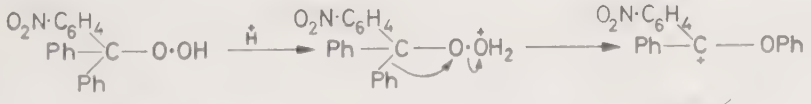
XV XVI XVII XVIII

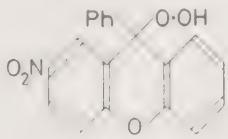


XIX XX XXI

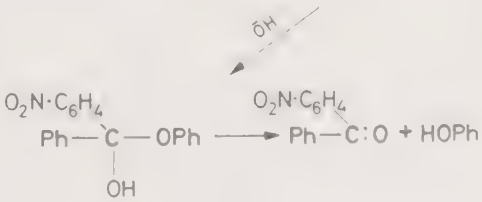
Throughout these reactions the nitro-substituent plays an important part. It secures initially the smooth formation of the ether linkage, (XV) → (XVI); it ensures ultimately the requisite scission of this linkage so that the catechol can be liberated, (XIX) → (XX); and it performs still another service. Consideration of the oxidation, (XIII) → (XIV), indicates that the entrant hydroxyl group becomes associated with an aromatic centre which is relatively rich in electrons: thus the product is the hydroxylated phenoxybenzophenone, and not xanthone accompanied by phenol. A similar feature characterizes acid-catalysed decomposition of *p*-nitrotriphenylmethyl hydroperoxide, which by an ionic mechanism (course 25) leads to *p*-nitrobenzophenone and phenol, whereas thermal decomposition, by a free radical mechanism, yields much *p*-nitrophenol and *p*-nitrotriphenyl carbinol[84]. The simple postulate of a hydroperoxide (XXII), or of a corresponding peracetate, completes the analogy with reaction (25) and provides a

(25)





XXII

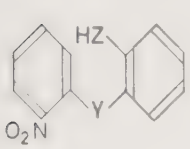


link with the Baeyer-Villiger type of oxidation mentioned on p. 59. Accordingly, the nitro group in the hydroperoxide (XXII), because of the restraint it imposes upon the electrons of the attached nucleus, ensures hydroxylation in the original phenolic nucleus unless the latter also is strongly de-activated.

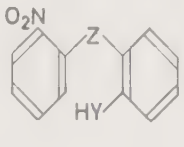
These provisions, therefore, lead to a simple three-stage synthesis of catechols from phenols. Of the three stages—ether-formation, hydroxylation, ether-scission—the second is the critical one in practice. In favourable cases the catechol ether, e.g. (XIX), crystallizes from the reaction medium in almost quantitative yield, but the reaction may miscarry through too rapid formation of organic peroxides. Little is known of these peroxides beyond that they precipitate as colourless, highly insoluble products and so withdraw material from hydroxylation. Fortunately this pitfall is easily avoided, either by maintaining in the acetic–sulphuric acid mixture a high proportion of the latter acid or, much better, by adding the hydrogen peroxide slowly and preferably as a solution in acetic acid. Thereby, using titration technique, it is often possible to follow the progress of the reaction through the colour changes incurred, the initial orange of the xanthylium salt being at first intensified and ultimately discharged to a pale straw yellow. With due attention to this major requirement considerable latitude is allowable in the experimental conditions, and catechol ethers of type (XIX) have been prepared from phenol; from mono-, di-, and trimethylphenols[79,82]; from *p*-isopropyl-, *p*-t-butyl- and *p*-t-octylphenols; from phenylphenols[82] and from halogenophenols[85]. From these ethers in turn a representative number of catechols have been obtained without difficulty.

It will be apparent that this method of preparing catechols can be extended to yield their monoalkyl ethers through alkylation of the intermediates of type (XIX). Normally alkylation would be effected in an alkaline medium, but here some complications arise. Sodium and potassium hydroxides convert 2-(2′-hydroxyphenoxy)benzophenone (XIV) into beautifully crystalline, golden yellow, hydrated salts[79] which have low melting points, are insoluble in 5N alkali, only moderately soluble in water and appreciably soluble in benzene or chloroform. These properties, indicative of covalent binding of the metal, are shared by alkali salts of the intermediates (XIX) and are sometimes disconcerting. They do not, however, prevent alkylation even in aqueous alkali where, for example, the catechol derivative (XIX) reacts with dimethyl sulphate to form the corresponding guaiacol derivative which

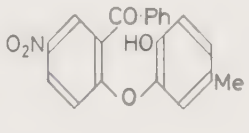
is also obtained as the condensate from guaiacol and 2-chloro-5-nitrobenzophenone. Another contingency is of greater consequence for reactions conducted in alkali. SMILES and his colleagues have shown that compounds of the general type (XXIII) may be rearranged[86] in an alkaline medium to their isomers of type (XXIV) and that, among other factors, this is conditioned by unequal ability in the dissimilar atoms Y and Z to supply electrons for the bond with the electrophilic nitrophenyl group. Although the special case where Y and Z are atoms of the same element was not then examined, it is clear that different donor capacities will exist in the two oxygen atoms of a catechol which is unsymmetrically substituted. Indeed the situation resembles that which provokes migration of the electrophilic acyl group in catechol mono-esters (*cf* p. 49). Rearrangement between the two catechol derivatives (XXV) and (XXVI) is therefore predictable, and it would be expected that the isomer which gives rise to the more stable anion would predominate in an alkaline environment.



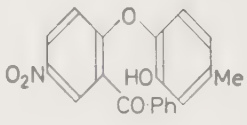
XXIII



XXIV

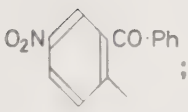


XXV



XXVI

R =



XXVII

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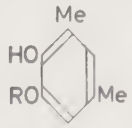
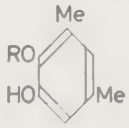


XXVIII



XXIX

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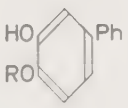
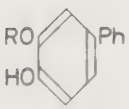


XXX



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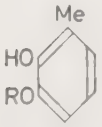
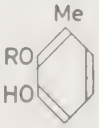


XXXI XXXII



XXXIII

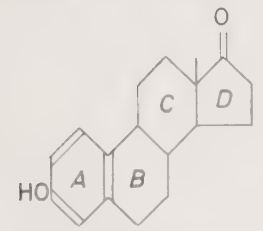
These predictions are fully confirmed[79]. Of the two compounds (XXV) and (XXVI), prepared from *m*- and *p*-cresol, respectively, the former is almost completely rearranged to the latter by dissolution in aqueous alkali: moreover, methylation of either by methyl sulphate in

alkali affords the same methyl ether, and that this is derived from (XXVI) is shown by its scission to 4-hydroxy-3-methoxytoluene. On the other hand, methylation without rearrangement is effected by diazomethane, the isomeric ethers corresponding to (XXV) and (XXVI) being obtained and identified. This kind of behaviour appears to be general: further examples[82] are provided by the isomeric pairs (XXVIII; XXIX), (XXX; XXXI) and (XXXII; XXXIII) where R represents the benzoylated nitrophenyl group (XXVII), and the second member of each pair as formulated is found to be the more stable in alkali. The behaviour of the last pair (XXXII) and (XXXIII) is particularly instructive. Only the isomer (XXXIII) can be synthesized by the hydroxylation procedure (it is formed from *o*-cresol, whereas from *m*-cresol the process leads to (XXV)): acidification of its solution in alkali yields a mixture of isomers (XXXII) and (XXXIII) with the latter greatly predominating; nevertheless, nearly complete rearrangement can be achieved by adding a trace of alkali to a fairly concentrated solution of the synthesized isomer (XXXIII) in methanol, whereupon the much less soluble isomer (XXXII) gradually crystallizes. The structures, (XXXII) and (XXXIII), assigned to these isomers are again confirmed by methylation with diazomethane followed by scission to the appropriate hydroxymethoxytoluenes which are otherwise known.

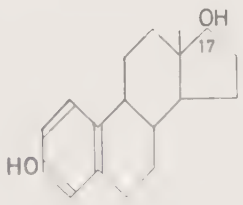
The evidence therefore indicates that in alkali there is equilibration between the two isomeric intermediates derivable from an unsymmetrically substituted catechol. The position of equilibrium is individually determined and appears to be reached fairly rapidly, so that methylation, for example, may give a unique product, but one of ambiguous structure. Accordingly, to be structurally reliable, alkylation in these cases has to be effected in a non-basic medium.

A particular application of the method deserves fuller description because of its intrinsic interest and the complexity of the molecules involved. During a study of the metabolites formed when labelled estrone (XXXIV) or estradiol (XXXV) is administered to humans, Kraychy and Gallagher[87] detected, by countercurrent distribution of the phenolic fraction of the urine, a peak of radioactivity which could not be attributed to any of the known urinary estrogens. Analysis and spectroscopic examination of the compound responsible suggested that it might be 2-methoxyestrone (XXXVII) and this was confirmed by synthesis *via* 2-nitro- and 2-amino-estrone, the diazotized amine being photochemically decomposed in methanol. The minute

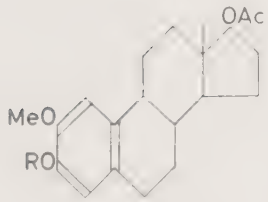
quantity thus made available was insufficient for the closer study merited by a compound of such origin and novelty. FISHMAN[88] therefore attempted its synthesis by *ortho*-hydroxylation of estrone. The aryl ether, obtained from estrone and 2-chloro-5-nitrobenzophenone, was submitted to the usual sequence of hydroxylation, methylation with diazomethane and scission by piperidine, but although the ultraviolet spectrum of the crystalline product was identical with that of 2-methoxy-estrone, the infra-red spectrum showed that ring D had been oxidized to a lactone structure. To avoid the vulnerable centre thus presented by the 17-ketone group, estradiol-17β (XXXV) was then chosen as starting point. The appropriate 3-aryl ether was prepared, the remaining and still vulnerable hydroxyl group at C_{17} was acetylated, and the hydroxylation–methylation–scission sequence was carried through, all of the intermediates being isolated and characterized. Thereby 3-hydroxy-2-methoxy-17β-acetoxy-estra-1:3:5(10)-triene (XXXVI; R = H) was obtained. Hydrolysis of this acetate gave 2-methoxyestradiol-17β which was also obtained by a variant in which the guaiacol type of intermediate (XXXVI; R = XXVII) was simultaneously hydrolysed and cleaved by potassium hydroxide in



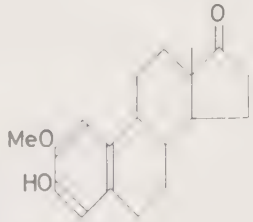
XXXIV



XXXV



XXXVI



XXXVII

ethanol. Oxidation of 2-methoxy-estradiol gave poor results, and a better method was found in hydrolysing the acetate group in (XXXVI; R = XXVII), oxidizing the resultant 17-alcohol to the 17-ketone, followed by cleavage with piperidine or alkali. By this remarkable and instructive series of operations 2-methoxyestrone was synthesized in upwards of 30 per cent overall yield.

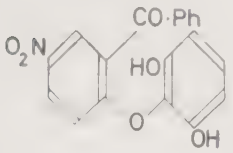
Pyrogallol Derivatives

From the time when these studies of *ortho*-hydroxylation were begun, it had been hoped to extend them to the preparation of pyrogallols from phenols through renewed hydroxylation of the intermediate catechol derivatives. This project pre-supposes, in the phenolic ring of the intermediate, a second free *ortho*-position with respect to the diphenyl ether link and there was encouraging significance in a test of this pre-requisite, which proved useful in course of the earlier work. Thus in cold concentrated sulphuric acid the compounds (XXIX) and (XXXIII) (p. 63) afford pale yellow solutions and are thereby easily distinguished from their respective isomers, (XXVIII) and (XXXII), which give bright red solutions indicative of xanthylium salt formation. Indeed, as events show, the rapidity of xanthylium salt formation and the protection afforded by the resultant positive charge nullify the risk of sulphonation in the phenolic ring.

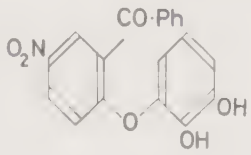
The second hydroxylating step proceeds normally[89]. A catechol intermediate, isolated from the first hydroxylation, is simply dissolved in cold concentrated sulphuric acid and the solution, diluted with acetic acid, is titrated with hydrogen peroxide, also in acetic acid. Thereby pyrogallol derivatives of type (XXXVIII) are smoothly obtained, and their monomethyl ethers are likewise available from guaiacol intermediates. Their dimethyl ethers can be formed subsequently by methylation with diazomethane.

At the scission stage, however, a complication is incurred. The net effect of warming compound (XXXVIII) in piperidine and removing excess of this reagent by an acid wash, is cyclodehydration to a highly coloured, crystalline product regarded as the fluorone derivative (XL). The course of the reaction in the basic environment must include (*i*) Smiles rearrangement of compound (XXXVIII) to its isomer (XXXIX) and (*ii*) cyclization of (XXXIX) expedited by the high reactivity in the ring which carries the phenolic anion. This interpretation is consistent with a number of facts. In the first place, scission is normal when applied to the mono- or di-methyl ethers derived from intermediates of type (XXXVIII): thereby 1- or 1:3-di-methyl ethers of pyrogallol and its homologues can be synthesized. It is again normal when applied to the di-*p*-tosylate prepared from (XXXVIII), in that this is split to a di-*p*-tosylate of pyrogallol. It is also normal for the particular intermediate (XLI) which, secured against cyclization by the blocking methyl groups, yields 4:6-dimethylpyrogallol. But it fails with the dibrominated intermediate (XLII) from which through

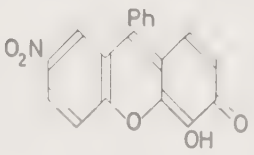
cyclization one bromine atom is displaced and the 2-bromo-derivative of the fluorone (XL) is formed. It also fails with the intermediates (XLIII), (XLIV) and (XLV) each of which, having available at least one free centre *ortho* to an hydroxyl group, undergoes cyclization to a homologue of the fluorone (XL).



XXXVIII

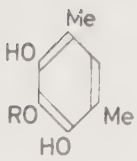


XXXIX

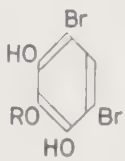


XL

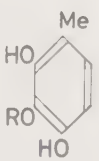
R = XXVII



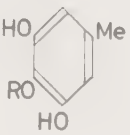
XLI



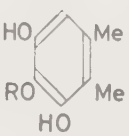
XLII



XLIII

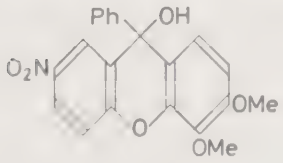


XLIV

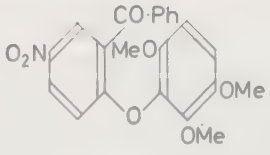


XLV

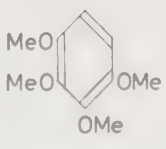
There is evidence[88] that the fluorone type of product is formed only or mainly during removal of excess of piperidine by treatment with mineral acid. When the wash with acid is replaced by a wash with water only, a tarry material is obtained. This reacts with mineral acid affording the fluorone whereas, on methylation with diazomethane, it yields the colourless xanth-hydrol (XLVI). Perhaps a closer study of the fluorone precursors would be rewarding, for it is not without interest that the xanth-hydrol, (XLVI), by successive hydroxylation and methylation, yields an intermediate (XLVII) which, after scission and renewed methylation, affords 1:2:3:4-tetramethoxybenzene (XLVIII). This compound, it may be noted, represents the third stage of hydroxylation starting from phenol and may presage developments of *ortho*-hydroxylation when combined with Smiles' rearrangement. None the less the immediate conclusion remains that pyrogallols, unlike their methyl ethers and unlike catechols, cannot generally be liberated from their intermediates by scission with piperidine.



XLVI

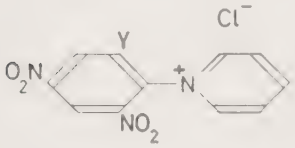


XLVII

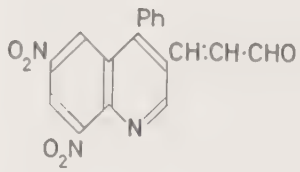


XLVIII

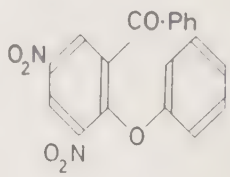
Fortunately the *ortho*-hydroxylation scheme is sufficiently flexible to allow of many variations, few of which have been examined systematically. Thus 2-chloro-5-nitroacetophenone can replace[85] the corresponding benzophenone for preparing catechol derivatives and its lower molecular weight could, on occasion, be an advantage. Again, resort to a dinitro-series derived from 2-chloro-3′:5-dinitrobenzophenone[79] could be the remedy for misdirected oxidation to phenol and a derivative of xanthone, if this were to occur in the mononitro series (*cf* p. 61). Another dinitro series, that derived from 2-chloro-3:5-dinitrobenzophenone, has been examined more extensively because of the advantages to be gained from the high electrophilic character of the dinitrated benzoyl ring.



XLIX



L

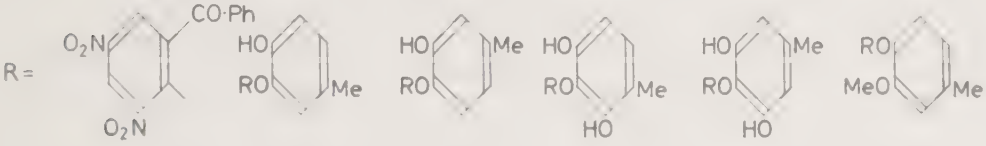


LI

In course of their work on the synthesis of thyroxin Hems and his colleagues[90] showed that pryidinium salts of type (XLIX), formed from a sufficiently reactive chloronitrobenzene in pyridine, react smoothly therein with phenols, yielding the appropriate diaryl ethers. About the same time Allan and Loudon[91] found that salts of this type in which Y is an acyl group, e.g. Y = PhCO·, are converted by aqueous alkali into 3-β-quinolylacroleins, e.g. (L). The latter reaction, however, does not occur in cold, dry pyridine wherein, accordingly, condensation of 2-chloro-3:5-dinitrobenzophenone with phenols may be effected very conveniently, aryl ethers of type (LI) being formed in high yield under very mild conditions. This is an important consideration where a precious phenol or an alkali-sensitive phenol is involved.

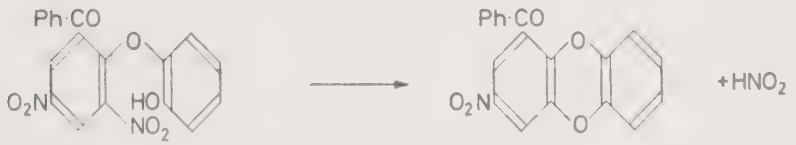
In this 3:5-dinitro series[92] mono- and di-hydroxylation, yielding dinitro intermediates of the catechol and pyrogallol types (e.g. LII and LIV), proceed without undue difficulty, although the compounds are all somewhat more sensitive than their mononitro analogues. Interest in them centres chiefly on the question whether their high reactivity can be turned to good account. In several respects the reactivity is too high. For instance the two isomers (LII) and (LIII), which by renewed hydroxylation give distinct products (LIV) and (LV), react with ethereal diazomethane to give the *same* methyl ether (LVI), identified by its scission to 4-hydroxy-3-methoxytoluene. This recalls

the similar methylation of 2-acetylalizarin to 1-acetylalizarin 2-methyl ether[93] and, from the structural point of view, makes methylation by diazomethane unreliable in this dinitro series. The dihydroxylated



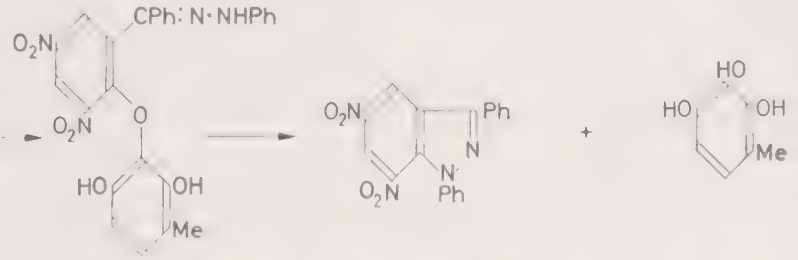
LII LIII LIV LV LVI

(26)



intermediates are still open to the risks that lead to fluorone formation, and to these there is now added another which is shared by the monohydroxylated intermediates, namely cyclization[94] to a dibenzodioxin as shown in reaction (26). This type of cyclization—analogous to the better known cyclization of some 2-hydroxy-2′-nitrodiphenylamines to phenoxazine derivatives[95]—occurs in warm piperidine, pyridine or alkali. These risks are reduced when the very vigorous interaction of piperidine and a hydroxylated intermediate of the 3:5-dinitro series is moderated by temperature control, by dilution with an inert solvent and especially by the presence of acetic acid. Although such expedients are partly successful, they do not provide a general solution to the problem, and this can be reached in another way.

(27) (LIV)



When phenylhydrazine (or hydroxylamine) reacts with an intermediate of type (LII) or (LIV), the initial attack appears to be directed to the carbonyl group, and the resultant phenylhydrazone (or oxime), which is not isolated, then undergoes cyclization with displacement of the hydroxylated nucleus (*cf* reaction 27) superseding elimination of

nitrous acid (*cf* reaction 26). Fluorone formation from dihydroxylated intermediates is not observed and, accordingly, scission by phenylhydrazine, in place of piperidine, yields the free pyrogallols of which the parent compound and its mono- and di-methyl homologues have so been prepared.

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3

THE CHEMISTRY OF DEXTRAN

*C. R. Ricketts**

INTRODUCTION

In recent years a substantial research effort has been devoted to the chemistry of dextran, partly on account of its fundamental interest and partly because of its application in blood transfusion as a plasma volume expander[1, 2], with the result that with starch and cellulose it is one of the most thoroughly explored polysaccharides. Some interesting features of its structure and biosynthesis have recently come to light.

* The author thanks Dr. R. K. Callow of the National Institute for Medical Research, London, for the infra-red spectra reproduced in *Figure 3* and Dr. Sheila Brooks and Professor M. Stacey, F.R.S. for reading the manuscript.

The main molecular chain of glucopyranose units joined by 1,6-linkages, *Figure 1*, carries branch chains, as shown in *Figure 2*. Branching affects

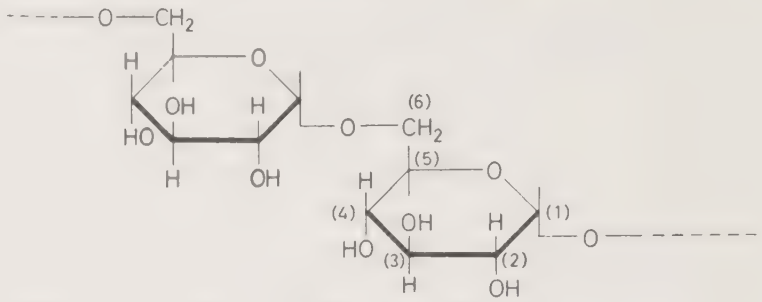
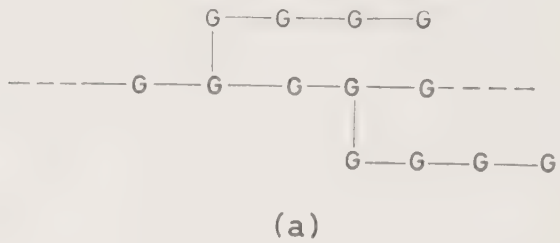


Figure 1. Two glucose units forming part of the molecular chain in dextran



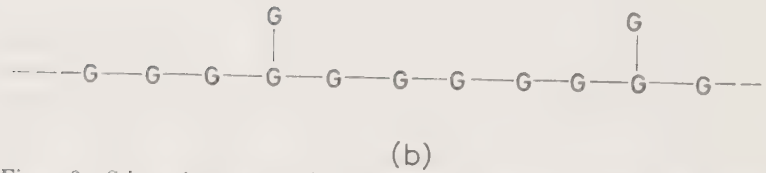


Figure 2. Schematic structure of two fragments of dextran molecules each having the same branching ratio. G represents a glucose unit

the physical properties of the dextran, and it is reasonable to suppose that it affects its interaction with biological systems also. The biosynthesis of dextran by bacterial enzymes acting on sucrose is to some extent analogous with the formation of polysaccharides of the starch class by phosphorylases acting on glucose-1-phosphate. Although the formation of branch linkages in the starch class of polysaccharides has been well explored, little is known of the enzymes responsible for branch linkage formation in dextran. This may be an opportune time to draw together the most recent ideas on dextran; STACEY and RICKETTS[3] have reviewed work up to 1950, and the present account is for the most part based on more recent publications.

STRUCTURE

Some twenty years ago the dextran produced by a strain of *Leuconostoc mesenteroides* was methylated[4] and the product was hydrolysed with

hydrogen chloride in methanol. The products of methanolysis were identified as 2,3,4,6-tetra-, 2,3,4-tri- and 2,3-di-*O*-methyl-methyl glucoside. These products were obtained in the molecular proportions of 1:3:1. Accordingly, a molecular chain of glucose units joined by 1,6-links with 1,4-branch linkages was proposed. The presence of the 2,3-di-*O*-methylglucose was maintained against criticism[5,6] and later independently confirmed[7]. It was for a time commonly assumed that all dextrans contained only 1,4-branch linkages. However, periodate oxidation of a highly branched dextran from *L. mesenteroides* N.R.R.L. B.742 and a relatively unbranched dextran from *L. mesenteroides* N.R.R.L. B.512 showed the presence of periodate-resistant glucose units in both dextrans[8,9]. On hydrolysis of the oxidized dextran these units yielded glucose. It was therefore suggested that these units carried branch chains at position 3 or at both positions 2 and 4. Burket and Melvin reported[10] that dextrans from various strains of *L. mesenteroides* showed, as dried films, varying amounts of absorption at 794 cm^{-1} (12·6μ) in the infra-red region of the spectrum. Furthermore the dextran produced by *L. mesenteroides* N.R.R.L. B.742 could be separated by graded precipitation with alcohol into two fractions, one of which showed increased absorption at this wavelength whereas the other showed none. These observations were correlated with the presence in the dextrans of periodate-resistant units[8,9,11].

Structure of Branched Dextrans

A full structural analysis[12] of the dextran formed by *Betacoccus arabinosaceous* (one of several strains of *L. mesenteroides*) has shown that in this dextran the branches are joined through 1,3-linkages almost exclusively. Methylation gave 2,3,4,6-tetra-, 2,3,4-tri- and 2,4-di-*O*-methylglucose in proportions corresponding to a chain length of 6–7 glucose units. Partial hydrolysis and fractionation of the resulting oligosaccharides yielded a disaccharide indistinguishable from 3α- or 3β-glucosyl-D-glucose. Hydrolysis of the periodate-oxidized dextran yielded glucose. The proportion of glucose in the mixture was in fair agreement with the amount expected from the results of methylation.

Infra-red spectra—A secure foundation for the interpretation of the infra-red spectra of dextrans has been provided by recent work[13–15] in which sugar derivatives have been systematically examined. The full publication[16] of the work on branched dextran referred to in the preceding paragraph includes also the confirmation of the presence of α-1,3-linkages in this dextran from its infra-red absorption. A

comparison[17] of the percentage of branched units, as determined by periodate oxidation titrations, with the infra-red spectra of four clinical dextrans is shown in *Figure 3*. The magnitude of the inflection at wave number 790–800 cm^{-1} is seen to be correlated with the percentage of branched units.

Figure 3. Comparable infra-red absorption spectra of four partially hydrolysed (clinical) dextrans showing the correlation between the percentage of branched units as determined by periodate oxidation and the absorption (left-hand ordinate) at wave-number 794cm⁻¹

Periodate oxidation—The use of periodate oxidation for the determination of dextran structure has been carefully evaluated in a series of papers from the U.S. Dept. of Agriculture laboratories at Peoria, Illinois. The oxidized dextran was hydrogenated and hydrolysed to a mixture of glycerol, erythritol and sorbitol. The proportions of these alcohols in the mixture were in several cases in fair agreement with the values predicted from titration[18]. Reasons for the exceptions were considered in detail. The possibility of 1,3- and 1,4-links occurring at intervals along the main molecular chain (see *Figure 4*) and not simply

at a branching unit was pointed out. The reliability of titration analysis was established[19] by experiment with the conditions of oxidation and with the analytical procedure. Dextrans having a high content of 1,4-links are liable to over-oxidation under the usual conditions. The work was then extended to the characterization and classification of dextrans from 96 strains of bacteria[20]. Solubility, intrinsic viscosity and some general information about the dextrans was recorded. The lower percentages of 1,4-like and 1,3-like linked units were within the limits of error of the periodate method; the highest percentages were about 50 and 40, respectively.

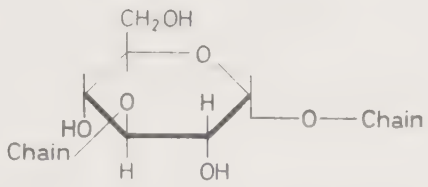


Figure 4. Illustrating the possible occurrence of a 1,3 glucosidic link in the main chain of a dextran molecule

Optical rotation—The specific rotation of dextrans differs with the solvent; for example a dextran showing +199° in water showed +203° in N potassium hydroxide and +215° in formamide. In general, there is an increase in optical rotation with increasing content of 1,3-linkages; between 0 and 40 per cent 1,3-like linkages the optical rotation, $[\alpha]_D^{25}$ in formamide, increases[20] from +210° to +235°. However, it appears from the range of values recorded that other factors also affect optical rotation. Taking the dextrans containing 0 and 35 per cent 1,3-links as model substances, the percentage of 1,3 links was estimated from infra-red absorption and compared with the percentage from periodate oxidation titrations; with few exceptions there was remarkably good agreement between the two values. A relationship between optical rotation and 1,3-branching in clinical dextran was calculated by Rowe[21] (see *Figure 5*). By extrapolation a value of −194·6° was obtained for a completely unbranched dextran.

Measurements of the molecular optical rotation of highly branched dextrans in cuprammonium solution have indicated the presence of 1,2-linkages[22] in these dextrans. Though detectable in principle by methylation, this kind of linkage is indistinguishable from the 1,4-linkage by periodate oxidation titration.

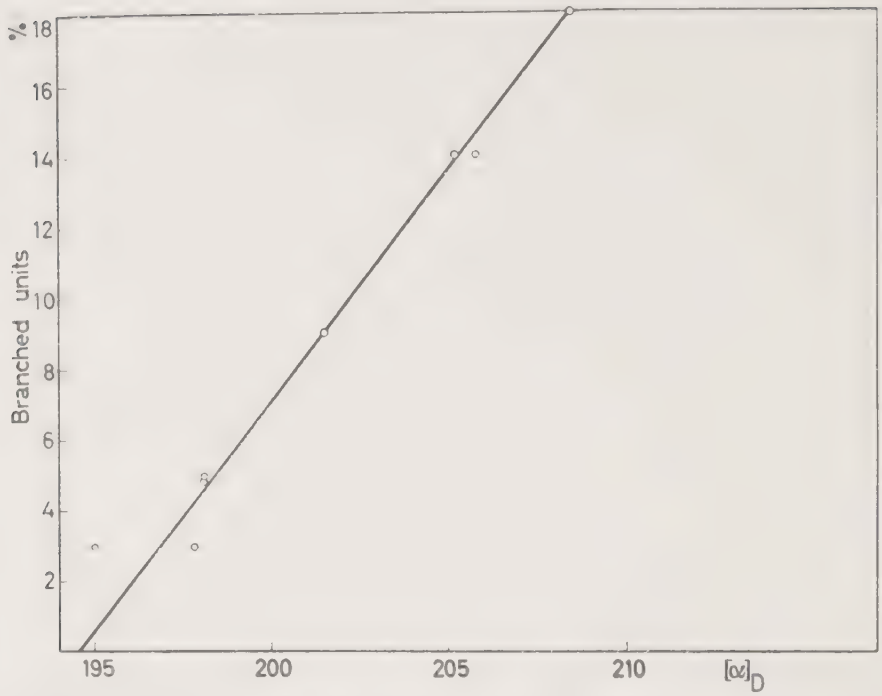


Figure 5. Showing the relationship between per cent 1,3 branch links in dextran and specific optical rotation

Structure of Relatively Unbranched Dextrans

The dextran produced when *Betacoccus arabinosaceous* is grown on a medium deficient in magnesium was shown[23] to contain an unusually small proportion of 1,3 links. The optical rotation, $[\alpha]_D^{19}$ +194°, is consistent with other observations of low values of optical rotation associated with low degrees of branching[11, 20]. From the methylated dextran 2,4-di-*O*-methylglucose was identified and distinguished from 2,3- and 3,4-di-*O*-methylglucose by paper chromatography and electrophoresis in borate buffer on paper. A very small amount of glucose was identified in the hydrolysate of the periodate-oxidized dextran. The infra-red spectrum showed no absorption at 794 cm^{-1} and therefore no indication of α-1,3-linkages. The authors conclude that the degree of branching in dextran is dependent on the composition of the culture medium and that magnesium favours branches, possibly because it is a component of the enzyme responsible for their formation.

A full structural examination of the dextran produced by *L. mesenteroides* N.R.R.L. B.512, the strain now used for the production of blood plasma substitute in the United States, Britain* and other countries,

* United Kingdom National Collection of Industrial Bacteria No. 8710.

has been completed[24]. The native dextran, of intrinsic viscosity 1·09 and molecular weight about 30 million, was methylated. A final methoxyl content of 45·4 per cent OMe (theoretical for fully methylated dextran, 45·6 per cent OMe) was attained, and the methyl dextran was shown by fractional precipitation to be homogeneous, there being little variation of specific rotation and intrinsic viscosity among the fractions. By hydrolysis under controlled conditions, 2,3,4,6-tetra-, 2,3,4-tri- and 2,4-di-*O*-methylglucose were obtained in the molecular proportions of 1:21:1. Side reactions occurring during hydrolysis of the methyl dextran were investigated using mixtures of the methylglucoses; the impurities formed included reversion products of 2,3,4-trimethylglucose. Some de-methylation was also observed. These side reactions were taken into account in arriving at the molecular proportions quoted. It was concluded that 91 per cent of the glucose units were linked through positions 1 and 6 and a further 4 per cent were non-reducing end-groups. Thus 95 per cent of the glucose units would be expected to yield formic acid on oxidation with periodate, and close agreement with this percentage was found experimentally. The remaining 5 per cent were believed from previous infra-red absorption measurements to be linked through 1,3 and 6 as branch points, and the results of periodate oxidation were consistent with this view. No 2,3-di-*O*-methylglucose was detected chromatographically, though control experiments showed adequate resolution of this substance. It was not possible to ascertain whether 2,3,6-tri-*O*-methylglucose, corresponding with a 1,4 main chain linkage, was present or not, as this substance was not resolved from 2,3,4-tri-*O*-methylglucose in the solvent system used. The range of formulae consistent with all the findings is illustrated in *Figure 6*. Recent evidence[25] obtained through determination of the yields of glucose, di-, tri- and tetra-saccharides on limited acid hydro-

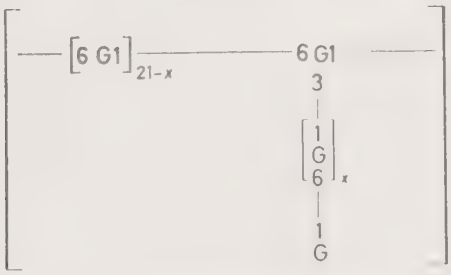


Figure 6. Illustrating range of formulae consistent with findings of Van Cleeve, Schaefer *and* Rist[24]. *Probably* $x = 0$ *and thus branches are a single glucose unit.* $G = \alpha$-D-*glucopyranose unit.*

lysis has indicated that at least 80 per cent of the branch chains consist of only a single glucose unit, i.e. in *Figure 6* $x = 0$.

The structure of certain partially hydrolysed and fractionated dextrans used clinically as blood plasma expanders in Canada, England, Sweden and the United States of America has been examined in detail by Jones and Wilkie[26], using the techniques of methylation and periodate oxidation.

BIOSYNTHESIS

Leuconostoc Cultures

Bacteria of the genus Leuconostoc grow well on media containing glucose, peptone and phosphate with additional B vitamins, notably thiamine, pantothenic acid, nicotinic acid and pyridoxin. Dextran is formed only when sucrose replaces glucose in the medium. Details of fermentation are to be found in the earlier papers reviewed in a previous article[3]. Dextran is separated from the culture fluid by precipitation with alcohol.

When cultures of *L. mesenteroides* B.512 are incubated beyond the maximum conversion of sucrose to fructose and dextran, some enzymic hydrolysis occurs resulting in dextrans of lower molecular weight[27, 28]. This strain also produces low molecular weight fructose polysaccharides, possibly levans. *L. mesenteroides* B.1146 shows neither of these characteristics.

Formation of Dextran by Cell-free Extracts

By filtration of cultures of *L. mesenteroides*, Hehre[29] obtained a cell-free extract which converted sucrose to a polysaccharide indistinguishable from dextran by serological tests. He suggested that the enzymatic formation of dextran might be expressed:

$$n \text{ sucrose} \longrightarrow \underset{\text{DEXTRAN}}{(\text{glucose})_n} + n \text{ fructose}$$

and pointed out[30] the analogy with levan formation

$$n \text{ sucrose} \longrightarrow \underset{\text{LEVAN}}{(\text{fructose})_n} + N \text{ glucose}$$

and amylose formation

$$n \text{ glucose-1-phosphate} \rightleftharpoons \underset{\text{AMYLOSE}}{(\text{glucose})_n} + \text{phosphate}$$

The known requirement of a ' primer ' or short-chain amylosaccharide as an acceptor of glucosyl groups in amylose formation indicated the possibility of a similar mechanism in dextran synthesis. In a review covering the whole field of enzymic synthesis of polysaccharides BARKER and BOURNE[31] point out that, since sugar phosphates are not formed[32] as intermediates in the conversion of sucrose to dextran, and since the sucrose cannot[29] be replaced by a mixture of glucose and fructose, it is probable that each step in the synthesis of dextran involves the exchange of the glucosidic link in sucrose for one in the polysaccharide, as follows:

$$\text{sucrose} + \text{enzyme} \rightleftharpoons \text{glucose-1-enzyme} + \text{fructose}$$

$$\text{glucose-1-enzyme} + \text{acceptor} \rightarrow \text{glucose-1-acceptor} + \text{enzyme}$$

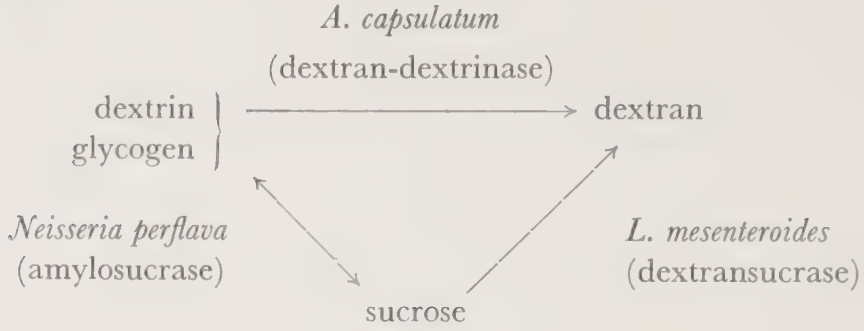
Light-scattering measurements[33] during the enzymic synthesis of dextran yielded extremely high values for the molecular weight, e.g. 50×10^6 rising to 175×10^6 at complete conversion of sucrose and after 22 h incubation at 25°C to 500×10^6. It was shown that the molecules are highly branched early in the reaction and become even more so as the reaction proceeds[34, 35]. These results are believed to be due to the formation of random long-chain branches by rearrangement of linear chains under the influence of a branching enzyme which is more heat stable than the polymerizing enzyme.

Bacterial Transglucosylases

A most interesting enzymic synthesis of dextran was investigated by HEHRE and HAMILTON[36]. A cell-free enzyme system from *Acetobacter capsulatum* was shown to convert dextrin (α-1,4-links) to dextran (α-1,6-links). In a further paper the mechanism of the synthesis was investigated, and the important concept of the transfer of a glucosyl group from dextrin to the non-reducing end of a growing dextran chain was put forward. Thereby this apparently anomalous conversion was brought within the scope of current theories of polysaccharide synthesis. The structure of the dextran produced from dextrin by *A. capsulatum* has now been fully confirmed[37]. The branching points involve positions 1 and 4, and the average chain length is about 13 1,6-linked glucose units.

HEHRE[38] has shown that an enzyme from *Neisseria perflava*, a gram-negative coccus sometimes found in the throat, can convert sucrose into

glycogen. Thus bacterial transglucosylases can effect the following conversions:



Dextran from Streptococci

The natural synthesis of a low molecular weight dextran by a strain of *Streptococcus* was reported by Hehre[39]. This dextran was shown to have a rather wide distribution of molecular weight with a substantial amount in the region of MW 50,000 to 60,000. Therefore, it is quite distinct from Leuconostoc native dextran which has a molecular weight of several million. The dextran from streptococcus was shown to have a non-reducing fructose unit instead of a reducing glucose unit.

Dextran has also been obtained[40] from cultures of *Streptococcus bovis* growing on a medium containing sucrose at 37 °C in the presence of carbon dioxide. On the evidence of periodate oxidation, infra-red absorption and optical rotation the dextran was unbranched. Growth of another strain of the same organism at a lower temperature or in the presence of magnesium still produced an unbranched dextran.

The Influence of Acceptor Molecules on Polymerization

Cell-free preparations of dextransucrase with high potency in converting sucrose to dextran have been obtained[41]. It has been shown that several simpler sugars can act as acceptor molecules when dextransucrase acts on sucrose, so that 1,6-linked oligosaccharides having the acceptor molecule at the end of the chain are formed[42]. Isomaltose, maltose, α-methylglucoside and glucose are efficient acceptors. These sugars increase the rate of the reaction through the simultaneous growth of many molecular chains. Fructose, leucrose (5-*O*-α-D-glucopyranosyl-D-fructose), melibiose and galactose are less efficient as glucosyl acceptors.

When short chain-length dextran of MW 5,000 mixed with dextransucrase was placed in a dialysis sac immersed in sucrose solution, the

slow diffusion of sucrose into the enzyme plus acceptor resulted in the formation of dextran with a bimodal distribution of molecular weight[43]. According to the amount of ' acceptor ' dextran present the molecular weight of the lower ' peak ' could be obtained in the range 39,000 to 325,000. In particular, using 2g acceptor dextran MW 5,000, 40g sucrose and 40,000 dextransucrase units, a dextran of MW 81,400 and therefore suitable for use as a plasma substitute could be synthesized directly. Thereby the partial hydrolysis of native dextran with its concomitant wide dispersion of molecular weight could be entirely avoided in the manufacture of clinical dextran. However, dextran of the desired low molecular weight was always accompanied by dextran of very high molecular weight which could be separated by fractional precipitation.

When *Betacoccus arabinosaceous* was grown on a sucrose medium with certain added salts, a high molecular branched (1,3- and 1,4-links) dextran was formed. The addition of 40 per cent glucose to the medium prevented growth; with 10 per cent glucose highly polymeric dextran was formed, but at 20 per cent glucose a mixture of isomaltose, isomaltotriose and higher homologues[44] resulted. There is evidence that an excess of sucrose also inhibits dextransucrase[45].

The kinetics of the transfer by dextransucrase of glucosyl groups from sucrose to α-methylglucoside, forming α-methyl isomaltoside and its homologues, were studied by Weibull[46]. The rate of the first step is lower than that of the succeeding ones which seem to be identical. The distribution of saccharides produced can be accounted for on the assumption that synthesis proceeds by step-wise transfer of glucosyl groups from sucrose to the growing polymer chain. An extensive theoretical treatment of the subject is given.

According to Bovey[47], the presence of α-methylglucoside increases the rate of formation of dextran and partly diverts the reaction from production of very high molecular weight polymer to the production of very low molecular weight polymer. He suggests that, in the absence of acceptor, the high molecular weight polymer is produced by an enzymic chain reaction, but in the presence of acceptor a non-chain reaction competes with the chain reaction. The proposition is formulated in some detail and shown to agree with some experimental observations.

The kinetics of dextransucrase action were also investigated by Stringer and Tsuchiya[48] who found that dextran synthesis required both sucrose and an acceptor. At sucrose concentrations exceeding 0·01M the initial rate depended on the availability of acceptor as well

as upon sucrose concentration. As a model acceptor α-methylglucoside was studied extensively. High sucrose concentrations in the absence of acceptor were found to inhibit dextransucrase, as HEHRE[49] had earlier reported.

Oligosaccharides formed by Transglucosylation

Several interesting saccharides are formed by transfer of glucosyl groups from sucrose to other sugars by the enzyme dextransucrase, and studies of these reactions have clarified the mechanism of dextran synthesis. The trisaccharide panose[50] is formed by transfer of a glucosyl group to maltose, yielding the structure G1,6G1,4G. In this reaction a 1,6-link has been created. Where the 6-position is difficult of access, as in the case of lactose, the glucosyl is transferred to position 2, yielding[51, 52] the structure: GAL 1,4[G1,2]G. This may be regarded as a branched trisaccharide, and it contains the 1,2-link recently synthesized[53] by prolonged heating of 1,2-anhydro-3,4,6-tri-*O*-acetylglucose; the 1,2 link may be present in some highly branched dextrans[22].

α-Methyl isomaltoside and its homologues are formed when α-methyl glucoside is the acceptor sugar[54, 46, 47]. Leucrose is formed by glucosyl transfer to the 5-position of fructose and occurs as a byproduct in dextran synthesis by *L. mesenteroides*[55] and *Strep. bovis*[56]. Transfer of glucosyl groups to 3-*O*-methylglucose, forming 6-*O*-α-D-glucopyranosyl-3-*O*-methyl-D-glucose and its homologues, has recently been demonstrated[57]. Similarly raffinose acts as an acceptor, a glucosyl group being transferred by dextransucrase to C(2) of the glucose unit in raffinose forming a tetrasaccharide[58].

A trisaccharide which may play a fundamental part in dextran synthesis was first obtained by the action of a cell-free extract of *Aspergillus niger* on a maltose–sucrose mixture[59]. The trisaccharide, which had the structure *O*-α-D-glucopyranosyl-(1 → 6)-*O*-α-D-glucopyranosyl-(1 → 2) β-D-fructofuranose, was evidently formed by the transfer of a glucosyl group from maltose to the glucose unit of sucrose. The trisaccharide was an effective acceptor of glucosyl groups transferred from sucrose by the enzyme dextransucrase yielding a homologous series of 1,6-linked oligosaccharides having the terminal fructose unit[60]. In contrast to sucrose the trisaccharide was not a substrate for dextransucrase, i.e. the enzyme did not remove glucosyl groups from it, and it is probable that the higher homologues similarly are not substrates for dextransucrase. If this is so, then unbranched dextrans must be built up by successive transfers of single glucose units, and transfers

of preformed chains are not involved. Such a fructose-terminated oligosaccharide would eventually lead to a dextran molecule carrying a terminal fructose unit. The fact that oligosaccharides do not accumulate when dextransucrase acts on sucrose alone may be due either to the operation of a single-chain mechanism or to a multi-chain mechanism in which a slow initial synthesis of trisaccharide is followed by rapid polymerization to dextran. The multi-chain mechanism in which formation of the trisaccharide is the rate-determining step appears at present to be the more likely hypothesis[60].

Purification of Dextransucrase

A method of preparing dextransucrase from *Betacoccus arabinosaceous* using cold alcohol precipitation has been devised[61]. It was not possible to desorb the dextransucrase from dextran, but the preparation was highly active in synthesizing a branched dextran when first prepared. After storage at 0°C for 2 months the enzyme preparation formed only unbranched dextran. The most likely explanation is that the preparation contained two enzymes, one of which was responsible for the synthesis of 1,6-links and the other, which was inactivated on storage, for the formation of 1,3-links.

Dextransucrase preparations from cultures of *Betacoccus arabinosaceous* on a medium containing maltose and sucrose contained only about one tenth of the dextran present when the organism was grown on sucrose alone[62]. This dextransucrase showed several differences from the heavily dextran-complexed enzyme. It was much more unstable to heat, more than half of its activity being lost after 3 days at 25 °C. Its optimum temperature of 25 °C and pH 5·0 differed little from dextransucrase of high dextran content. Dextransucrase of low dextran content exhibited only slight activity when incubated with sucrose alone. The addition of maltose (as acceptor) increased the rate of fructose production by 300–400 per cent. In the presence of other sugars, particularly isomaltose, methyl α-D-glucoside and D-glucose, the rates of fructose production were proportionately higher than those with dextransucrase of higher dextran content.

Dextransucrase has also been isolated by ammonium sulphate precipitation from cell-free culture fluids of *Streptococcus bovis* grown on sucrose or glucose in the presence of carbon dioxide. The enzyme isolated from sucrose cultures contained 70 per cent polysaccharide and 1·79 per cent nitrogen, but the enzyme from glucose cultures contained only 4 per cent polysaccharide and 9 per cent nitrogen. Both preparations

had maximum activity in the range pH 5 to 6·5 and in the temperature range 37–44° C. Transfer of glucosyl groups to a variety of acceptor molecules was demonstrated[63]. The effect of *p*H upon enzyme activity has been examined in detail[64].

Neely[65] has subjected dextransucrase to a photo-oxidation technique which is known to destroy the imidazole portion of histidine in proteins. He found that enzyme activity was decreased, showing that the catalytic activity was closely associated with the imidazole group in the dextransucrase molecule.

POLYMER PROPERTIES

A detailed discussion of the physical chemistry of macromolecules and its application to dextran is outside the scope of this chapter but, because of the importance of molecular weight distribution in determining the properties of any sample of dextran or its derivatives, some of the principal conclusions are mentioned.

Viscosity–Molecular Weight Relationships

The first physico-chemical investigation of dextran was reported in 1944 by Grönwall and Ingelman[66]. Using the ultracentrifuge they measured sedimentation and diffusion constants and concluded that the molecular weight of native dextran was of the order of several million. Ingelman and Halling[67] partially hydrolysed native dextran, obtaining preparations highly polydisperse in molecular weight. By fractional precipitation with alcohol more homogeneous fractions were obtained. Sedimentation and diffusion measurements on these allowed molecular weights to be calculated and compared with intrinsic viscosity measurements. For the range of molecular weights 40,000 to 300,000 they obtained the relationship

$$[\eta] = 8{\cdot}2 \times 10^{-7}\,\mathrm{M} + 0{\cdot}18$$

The dextran investigated was produced by the Swedish VII E strain of *L. mesenteroides* (reference 2, p. 40). Wales, Marshall and Weissberg[68] determined Mw by the sedimentation equilibrium method for the dextran produced by *L. mesenteroides* B.512. Mn was determined by end-group assay. Mv was then calculated and the relationship

$$[\eta] = 10^{-3}\,\mathrm{Mv}^{0{\cdot}5}$$

was shown to hold over the range of molecular weight 20,000 to 250,000. Wallenius and Granath[69] found a similar relationship for dextran produced by the B.512 strain.

Investigations of the influence of the degree of branching in the dextran molecule upon the relationship between intrinsic viscosity and molecular weight have now been reported from several laboratories[70–75]. Ogston and Woods[76] found a wide range of sedimentation coefficients in dextran fractions and calculated some molecular weight distributions. They concluded that dextran molecules in solution are highly hydrated and nearly spherical in shape. Mention should also be made of light-scattering experiments by Granath quoted (by Grönvall[2]), showing for a dextran with 15 to 20 1,6-links per one non-1,6-link a relation

$$[\eta] = 2{\cdot}18 \times 10^{-3}\ \mathrm{Mw}^{0{\cdot}43}$$

and for a more branched dextran having only 2 to 3 1,6-links per one non-1,6-link the relationship

$$[\eta] = 4{\cdot}4 \times 10^{-3}\ \mathrm{Mw}^{0{\cdot}34}$$

In deriving molecular weight from an intrinsic viscosity measurement it is essential to take account of the branching ratio of the dextran. It is also worth noting the exact conditions of viscosity measurement, the type of viscometer used, the temperature and concentrations at which measurements were made and the method of calculating intrinsic viscosity. In principle, the molecular weight distribution should be of the same form in the sample under investigation and in the fractions used to construct a calibration graph of intrinsic viscosity and Mw; only Mv is measured unequivocally by intrinsic viscosity. Some molecular weight determinations on clinical dextrans are reported[77] from the National Bureau of Standards, U.S.A., where accurate determinations of optical rotation, refractive index and density of dextran solutions have been made[78]. A method for evaluating the reliability of routine determinations of molecular weight distribution in clinical dextrans has been described[79], and a useful paper on the physico-chemical characterization of clinical dextran should also be mentioned[80].

End-group Assay and Osmometry

Number average molecular weights have been determined by methods utilizing the reducing power of the end-group[81] and by the addition of

^{14}C-cyanide ions to the reducing group[82]. Methods of partial depolymerization of native dextran which involve heating the dextran to temperatures above 100° C in aqueous or glycerol solution[83] may cause reactions at the reducing end-group, e.g. glucoside formation with glycerol, and to these samples such methods are clearly inapplicable. Osmometry offers an alternative but the pore size of the membranes is of critical importance. Small molecules of a polydisperse sample may leak through the membrane; if the pores are smaller the time to reach equilibrium is unduly prolonged. An improved osmometer designed by Rowe[84] overcomes these difficulties to some extent and has been applied to dextran solutions (Squire *et al.*[1], p. 36) and to serum–dextran mixtures. The interaction of dextran with human serum albumin was also investigated by Wales, Rothman, Stasny and Weissberg[85]. Osmotic pressure measurements on dilute solutions of dextran fractions with a branching ratio of 1:12·5 were made by Mariani and co-workers[86] in the range of Mn 93,000 to 172,000; reasons for the slope of the plot of π/c against c are discussed in detail.

Other Physico-chemical Studies

Electron microscope pictures showing long, threadlike dextran molecules were made by Ingelman and Siegbahn[87]. X-ray powder photographs by Jeanes, Schieltz and Wilham[88] showed a remarkable degree of molecular orientation in powdered dextran exposed to a humid atmosphere. A novel method of examining dextran by thermal decomposition has been reported[89]. Electrophoresis of clinical dextrans in free solution in borate buffer showed mobility proportional to molecular weight in the range 18,000 to 60,000; two components were detected in some dextrans[90].

Depolymerization of Dextran

The depolymerization of dextran has received a good deal of attention. In addition to methods already mentioned, depolymerization can be brought about by hydrogen peroxide[91], ultrasonic waves[92,93] and an alternating electrical field[94].

High molecular-weight dextran has been irradiated[95] in dry form with 800 kV peak electrons. The product was examined by light scattering, viscosity and reducing end-group analysis. The results indicated that irradiation causes extensive degradation accompanied by considerable branching. The evidence for branching in the product is derived from measurements of viscosity and molecular weight.

Irradiation of aqueous solutions of dextran with gamma rays from Co^{60} was investigated by PHILLIPS and MOODY[96] who used chromatography combined with isotope dilution to elucidate two independent processes in the degradation: first, hydrolysis to glucose and oligosaccharides accompanied by secondary reactions of the glucose forming erythrose, glyoxal and glyceraldehyde, and secondly, oxidation forming gluconic and glucuronic acids. There was more hydrolysis in absence of air and more acid production when oxygen was present.

The action of mould enzymes[97] yields isomaltose and isomaltotriose[98]. Random scission of glucosidic linkages may occur[99] with some mould enzymes. Three strains of *Lactobacillus bifidus* have been shown[100] to secrete an extracellular dextranase. The enzyme was isolated by precipitation with ammonium sulphate and showed maximum activity in the range pH 5·4–6·5 and in the temperature range 40–50 °C. The products of this enzyme were a mixture of isomaltotriose, tetraose, pentaose and higher oligosaccharides. Glucose and isomaltose were not produced. A tetraose and a pentaose probably containing the α-1,3-branch link from the original dextran have been separated[101] by chromatography on paper of a digest of this dextranase with dextran containing 12–15 per cent α-1,3-links.

DERIVATIVES OF DEXTRAN

Esters or ethers involving the hydroxyl groups of dextran provide macromolecules with very diverse properties. They may be electrically charged, negatively or positively, or neutral. Their properties depend on the degree of substitution in the parent molecule and the molecular weight distribution. It will be convenient to consider these derivatives under the headings: anionic polyelectrolytes, cationic polyelectrolytes, metal complexes and borate and phosphate complexes.

Anionic Polyelectrolytes

The ester of dextran with sulphuric acid may be prepared by mixing chlorosulphonic acid with pyridine at about −10 °C, raising the temperature to 60 °C and adding the dry, finely ground dextran[102, 103]. The reaction is heterogeneous, the powdered dextran dissolving to form a lower viscous layer. The reacting entity is probably the pyridine sulphur trioxide complex which can be obtained in crystalline form from the same reagents[104]. Good yields of sodium dextran sulphate containing 14–18 per cent sulphur, corresponding with 1·3 to 2·2

sulphate groups per glucose unit, are readily obtained. Dextran sulphates with molecular weights ranging from several million down to the oligosaccharide esters have been prepared[105]. Decreasing the proportion of sulphating reagents yields products with a lower degree of sulphation, and these may be heterogeneous with respect to sulphur content. Graded precipitation of the cetyl trimethyl ammonium salt from strong sodium chloride solution by adding water yields fractions which are more homogeneous in degree of sulphation than the original material[106]. Alkaline hydrolysis of dextran sulphate and subsequent acidic hydrolysis yields altrose, gulose and mannose[107] as well as glucose. Formation of altrose and gulose is readily explicable in terms of epoxide ring intermediates, and the migration of an epoxide ring was invoked[108] to explain the formation of mannose.

The dextran sulphates exhibit a remarkably wide range of biological properties, mainly of interest in the medical field, and it will only be possible to mention outstanding examples. In addition to blood anti-coagulant activity[109–111] a lipaemia clearing effect on blood plasma has been observed[112–114]. Precipitation of fibrinogen by high molecular-weight dextran sulphates allows human anti-haemophilic globulin to be isolated in a purer form[115]. Addition of high molecular-weight dextran sulphate to serum precipitates the β-lipoproteins and permits their rapid isolation without oxidation by air[116]. Thus the high MW dextran sulphates which are toxic because they precipitate blood proteins may be put to good use in isolating them. Low MW dextran sulphates with high sulphur content show anti-coagulant activity which can be therapeutically useful, but where the lipaemia clearing effect is required without anti-coagulant activity the low MW, low sulphur content dextran sulphates may be applicable.

The carboxymethyl ether of dextran may be prepared[117] by reaction of dextran in strong sodium hydroxide solution with sodium monochloroacetate. The carboxyl group so introduced is attached to the macromolecule by an ether linkage and is therefore extremely stable. The viscous properties of the resulting macromolecular polyelectrolyte have been measured[118]. Some phosphoric acid esters of dextran have been reported[119].

Cationic Polyelectrolytes

Molecules of this type are not commonly encountered. A cationic group may be introduced into dextran by reaction with 2-chlorotriethylamine in alkaline solution[120, 121]. Thereby the tertiary amino

group is firmly attached to the macromolecule through an ether linkage. The product may be isolated as the hydrochloride or free base. The latter readily forms a quaternary compound with methyl iodide. In view of the interesting biological properties of the negatively charged dextran sulphates, the properties of these positively charged basic dextrans may be worth exploring. Under specified conditions soluble or insoluble complexes are formed with blood plasma proteins[121]. Insoluble salts are formed with sulphated mucopolysaccharides such as heparin. Suspensions of bacterial cells or of red blood cells, the stability of which depends to some extent on the net electronegative charge of the cell surface, are agglutinated by these positively charged macromolecules.

Metal Complexes

Numerous instances of the formation of complexes between sugars or sugar alcohols and the metals of groups 1 and 2 in the periodic table of elements are known. In particular, complexes of the cuprammonium ion with sugar derivatives and with cellulose have been extensively studied. In strongly alkaline solution dextran forms insoluble complexes of uncertain structure with a wide range of metal cations[122], e.g. Pb^{++}, Bi^{+++}, Fe^{++}, Fe^{+++}, Cu^{++}, Ce^{+++} and UO_2^{++}. The complex which separates on shaking an alkaline solution of dextran containing cupric copper and citrate is sufficiently reproducible in composition to form the basis of a method of estimating dextran[123].

The complex of dextran with ferric iron can be obtained in a form which is stable and soluble in neutral solutions. There is some doubt as to whether the solution should be regarded as a ferric hydroxide sol having dextran as the stabilizing colloid or as a complex of more definite composition. The iron complex of dextran originally showed great promise[124] in medicine as a source of iron for the formation of haemoglobin[125], but confirmation[126] of a carcinogenic effect[127] in some species of animals has resulted in medical use of the iron complex being regarded more critically[128,129].

The complex of dextran with Ca, Sr or Ba provides a novel method of fractionating dextran for molecular size[130]. The dextran complex is precipitated from a solution of the metal hydroxide, e.g. $Ba(OH)_2$. The precipitate is redissolved by fractional acidification of a well stirred suspension. The high molecular-weight dextran complex is dissolved first, the fractional solution process being interrupted for separation of fractions as required.

Borate and Phosphate Complexes

It would appear that in alkaline solution loose complexes are formed between phosphate or borate anions and dextran.

Homogeneous fractions of dextran dissolved in borate buffer pH10 are reported[131] to show an electrophoretic mobility dependent on the molecular weight of the dextran. The molarity of the buffer is important; the greatest differences in mobility were found in the range 0·045 M to 0·085 M.

The solubility of dextran in ethanol–water solution is increased by very low concentrations of anions but decreased by moderate concentrations[132]. Phosphate has a particularly strong precipitating effect[133]. The addition of 0·6 per cent trisodium phosphate to a solution of dextran in ethanol–water at the point of incipient turbidity precipitates the dextran from solution[134].

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4

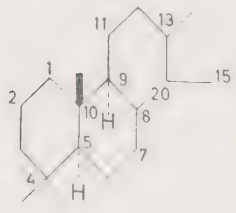
THE CHEMISTRY OF THE HIGHER TERPENOIDS

J. A. Barltrop and N. A. J. Rogers

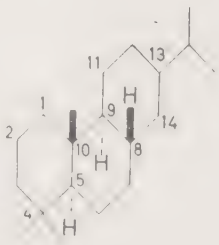
The chemistry of the di- and triterpenoids has been amply covered up to 1958 by de Mayo[1]. Since that time, there has been no systematic review, although many points of interest have been covered by Tsutsui[2]. The present survey makes no attempt to be exhaustive, the authors having chosen rather to deal with selected topics in detail. Thus only the recent intensive work on certain groups of diterpenoids and the present position with regard to the biosynthesis of the higher terpenes is discussed. No mention is made here of the many recent essays in total synthesis, since this topic will shortly be dealt with elsewhere[3]. For reasons of space, the complex chemistry of gibberellic acid is not examined, and the diterpenoid alkaloids, having been ably reviewed recently[4, 5], are not mentioned further.

Numbering System

In this review, the lead of de Mayo[1] will be followed, and the numbering of all diterpenes will be brought into line with that of the steroids and triterpenoids, and based on the hydrocarbons labdane (I), abietane (II), pimarane (III).



I



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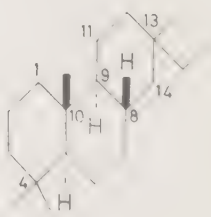


III

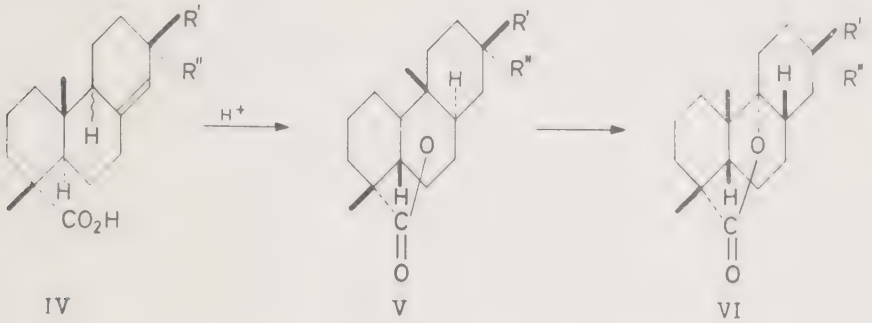
PIMARIC ACIDS

Dextropimaric and isodextropimaric acids have now been renamed, more simply, pimaric and isopimaric acids[6–8].

It had been suggested that these acids are epimeric at either carbon atom 13 (HARRIS and SANDERSON[9]) or 9 (WENKERT[10]). A considerable body of evidence has now been assembled which indicates that they are, in fact, epimeric at both of these centres.

The work of four groups[6–8, 11] has shown, using essentially the same method, that the acids are at least epimeric at $C_{(13)}$. Thus, with concentrated sulphuric acid, both acids give abietic acid, although in low yield. This demonstrates their identity at centres 4, 5, and 10.

In the case of the dihydroacids, this treatment leads to the formation of different pairs of γ- and δ-lactones (V and VI, R′, R″ = Me, Et).

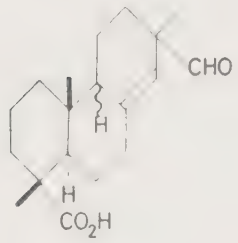


IV V VI

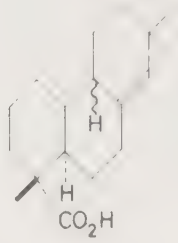
Thus, since all asymmetric centres, with the exception of $C_{(4)}$ and $C_{(13)}$, are perturbed during these transformations, the two pimaric acids must be epimeric at $C_{(13)}$.

Equilibration of the lactones (V) and (VI) with concentrated sulphuric acid led to slightly different percentages of the δ-lactone: $95 \pm 0{\cdot}6$ per cent from dihydropimaric, and $96{\cdot}4 \pm 0{\cdot}8$ per cent from dihydroisopimaric acid. It was argued[6] that, since the δ-lactone is stabler than the γ-lactone, and since the change (V $\rightarrow$ VI) involves a conformational inversion at $C_{(13)}$, then the smaller percentage of δ-lactone should arise in that case where the bulkier ethyl group moves into the axial conformation (β). In other words, dihydropimaric acid is (IV, R′ = Et, R″ = Me) and dihydroisopimaric acid is (IV, R′ = Me, R″ = Et). While this argument is sound, the difference in the yields of the lactones is so small, and the intrinsic difficulties of the determinations are so great that the results must be regarded with some caution.

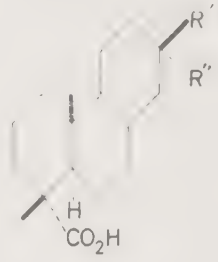
From surface tension measurements[12], it has been concluded that the vinyl group is quasi-axial in pimaric acid and quasi-equatorial in isopimaric acid. This result supports the above conclusion, but again it should be treated with reserve, since it was based on the assumption that the 10-methyl and 9-hydrogen are in the *trans*-arrangement in both acids. This is now known not to be the case.*



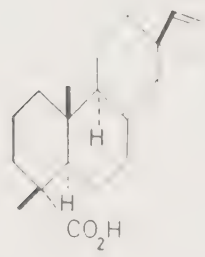
VII



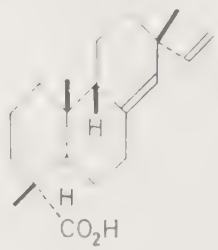
VIII



IX



X



XI

Recent mass-spectrometric[13] and infra-red[14] studies have suggested that pimaric and isopimaric acids are epimeric at $C_{(9)}$. This has now been proved in the following manner. By reaction with osmium tetroxide, followed by periodate oxidation, pimaric and isopimaric acids were converted[15] into the aldehydes (VII) which, on Wolff-Kishner reduction, gave two different acids (VIII).

From the supposed stability of pimaric acid to mineral acid, a *trans-anti*-arrangement at carbon atoms, 5 10, and 9 has been suggested[11]. However, it has now been shown that both pimaric and isopimaric acids can be isomerized by hydrogen chloride in chloroform to the acids (IX, R = vinyl, Me)[8]. The rather greater ease of migration of the double bond in dihydroisopimaric acid, compared with dihydropimaric acid, may be advanced as evidence in favour of a 9(β)-hydrogen in isopimaric acid[8,15], but it is possible that this difference is, in

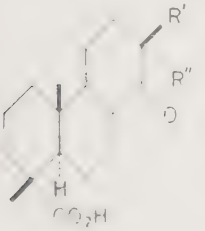
* See section on sandaracopimaric acid and rimuene for confirmation of these assignments.

part at least, a reflection of the different configuration of the two acids at $C_{(13)}$. A more convincing picture is likely to emerge from a kinetic study of the double-bond migration to the acids (IX). This work is apparently in hand[15]. Recent optical rotatory dispersion (ORD) studies[16] have given considerable support to the suggestion that pimaric acid has a 9(α)-hydrogen, and isopimaric acid a 9(β)-hydrogen.

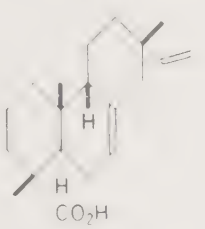
To sum up, it is certain that pimaric and isopimaric acids are epimeric at carbon atoms 9 and 13, and the most likely structures for these acids, on the evidence available at present, are (X) and (XI), respectively. Some doubt remains about the configuration of these acids at $C_{(13)}$, and this point is discussed later under rimuene.

Neoisodextropimaric Acid

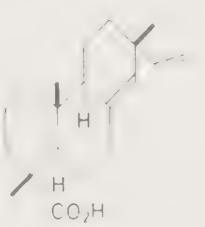
This acid[18], isolated from the fruits of *Juniperus rigida* and *J. conferta*, was originally suggested to be (IX, R = vinyl, Me), because oxidation of the dihydroacid gave[19] the compound (XII). However, neither of the dihydropimaric acids (IX, R = Et, Me) was identical with the new dihydroacid[8], which is now believed to be the Δ^7-isomer. The infra-red spectrum of the dihydroacid, showing bands typical of a trisubstituted double bond, supports this contention. Further, the dihydroacid is readily isomerized by acid to Δ^8-dihydroisopimaric acid. The ORD curve of the dihydroacid[16] suggests structure (XIII) or (XIV) for the new diterpenoid. Since (XIV) is now known to be the structure of sandaracopimaric acid (see below), it follows that neoisodextropimaric acid (' Ukita's acid ') is represented by structure (XIII).



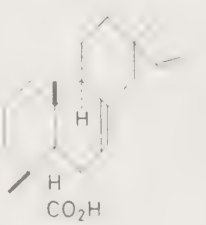
XII



XIII



XIV



XV

Sandaracopimaric Acid

This acid, isolated from the N. African 'sandarak' tree, *Callitris quadrivalvis*[20], has been the subject of a recent study[21]. Dehydrogenation of dihydrosandaracopimaric acid gave the naphthalene (XXIV) antipodal to that obtained from dihydropimaric acid[20c]. Degradation to the acid (VIII), related to pimaric acid, and rearrangement of the

dihydroacid to the acid (IX), related to isopimaric acid, make it probable that sandaracopimaric acid is represented by the structure (XIV). The conversion of the acid to rimuene[20c] provides confirmation for this structure (see below).

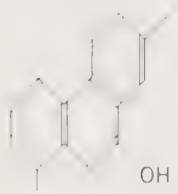
Cryptopimaric Acid

This acid[22], another isomer of pimaric acid, has been shown to have the same configuration at $C_{(9)}$ as that acid[13]. It is probable, therefore, that cryptopimaric acid is a double-bond isomer of pimaric acid, possibly (XV), in which the stereochemistry at $C_{(13)}$ is undefined. The ORD curve of the dihydroacid[16] supports this view.

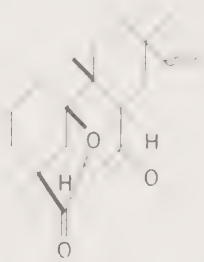
Rosenonolactone

This diterpenoid, a metabolite of *Trichothecium roseum* Link, was originally isolated, together with smaller quantities of closely related compounds, by ROBERTSON and his group[23, 24].

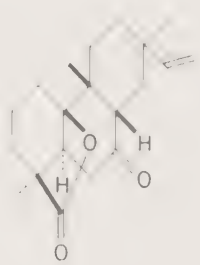
Rosenonolactone exhibited in its ultraviolet and infra-red spectra bands characteristic of an isolated carbonyl group, a vinyl group and a γ-lactone. Selenium dehydrogenation gave rise to 1,7-dimethylphenanthrene and to 1,7-dimethyl-9-phenanthrol (XVI). The production of this phenol located the carbonyl function at $C_{(7)}$.



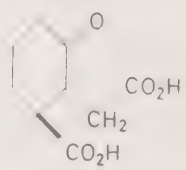
XVI



XVII



XVIII



XIX

Rosenonolactone, under basic conditions, is in equilibrium with a second lactone, isorosenonolactone, the equilibrium involving inversion of the $C_{(8)}$-hydrogen.

Reduction to a triol[25], which gave a diacetate and was resistant to periodate oxidation, together with the previous information, suggested the gross structure (XVII) for these lactones. The fact that dihydrodeoxorosenonolactone could not be related to the γ-lactones (V) from either pimaric or isopimaric acid indicated that the lactone and 9-methyl groups were in a *cis*-relationship.

The more hindered nature of the carbonyl group in isorosenonolactone suggested a *trans-syn-cis* arrangement (XVIII), rosenonolactone having the *trans-syn-trans* structure (XVII).

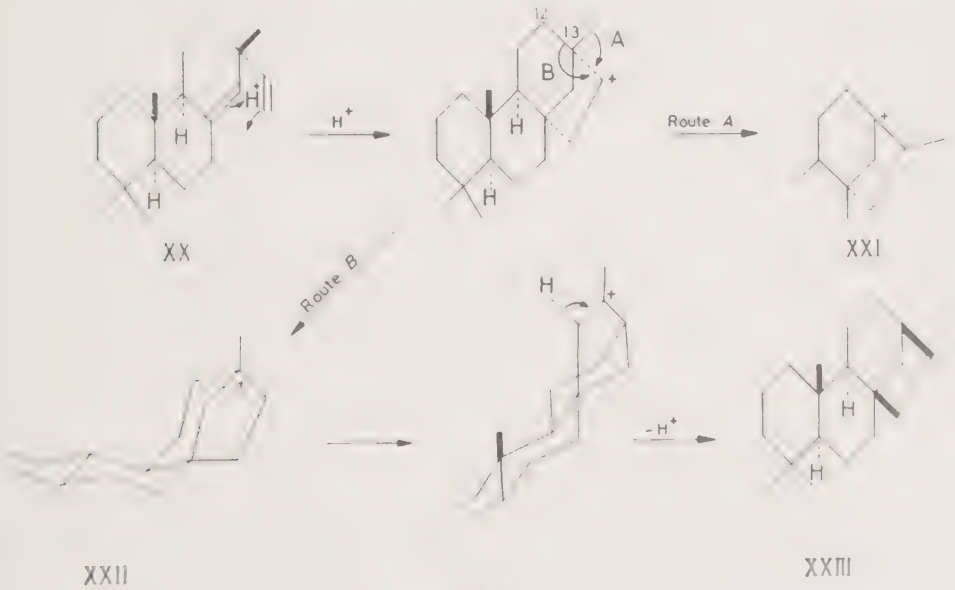
Comparison of the ORD curve of the C_{10}-ketodiacid (XIX), obtained by degradation of rosenonolactone[26], with that of a similar compound of known absolute configuration confirmed that (XVII) represents the absolute configuration of rosenonolactone, the stereochemistry at $C_{(13)}$ being undefined.

DITERPENE HYDROCARBONS

Rimuene

The early structural investigations on this tricyclic diterpene, isolated from the essential oil of the New Zealand 'rimu' tree (*Dacrydium cupressinum*), have been reviewed by BARTON and SIMONSEN[27].

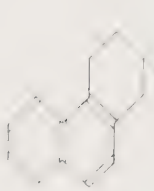
More recently[28], rimuene has been partially dehydrogenated to the compound (XXIV), identical with that obtained under similar conditions from the pimaric acids. The production of this compound locates the position of the vinyl group at $C_{(13)}$. The second double bond was located by treating dihydrorimuene with perbenzoic acid and reacting the resulting oxide with methyl magnesium iodide. This led to the formation of the alcohol (XXV), which, on selenium dehydrogenation, gave the known 1,2,8-trimethylphenanthrene (XXVI). Thus, the carbon skeleton of rimuene must be that shown in structure (XX), without its stereochemical implications.



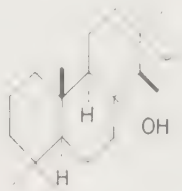
XX XXI XXII XXIII

The conversion[29] of rimuene to the abietadiene (XXVII), identical with that obtained from abietic acid, allowed the stereochemistry at carbon atoms 5 and 10 to be defined. The acid-catalysed rearrangement of rimuene to isophyllocladene (XXIII, see below) permits of an assignment of configuration at $C_{(13)}$ in rimuene. This reaction, which may or may not be concerted, can in principle proceed by migration of the $C_{(13)}$-methyl group (route *A*) or of $C_{(12)}$ (route *B*). Route *A* is improbable because it involves an energetically unfavourable bridgehead carbonium ion (XXI) (*cf* the apocamphyl halides[30]). Route *B* can give rise to the *β*-oriented 5-membered ring of isophyllocladene *via* an ion[31a] (XXII) only if the $C_{(13)}$-vinyl group in rimuene is *α*-oriented.

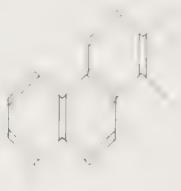
Hence the complete structure of rimuene may be written as in (XX). This assignment confirms the structures given to the various pimaric acids (see above) in view of the successful conversion of sandaracopimaric acid into rimuene[20c] and the conversion of pimaric acid into a hydrocarbon not identical with rimuene[17].



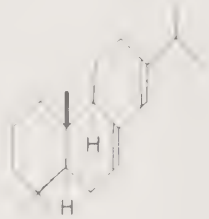
XXIV



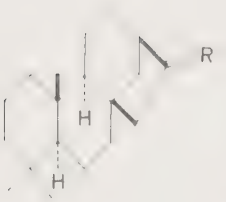
XXV



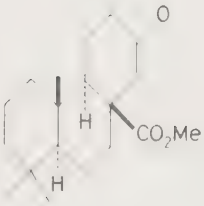
XXVI



XXVII

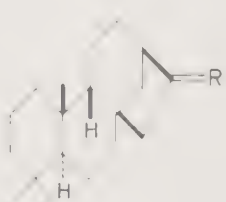


XXVIII



XXIX

XXX



XXXI

Phyllocladene

The chemistry of this fairly widely distributed hydrocarbon has been reviewed by Barton and Simonsen[27]. It is tetracyclic and contains one double bond which, on ozonolysis, gives rise to formaldehyde and a nor-ketone (XXVIII; R = O). Acid-catalysed rearrangement to isophyllocladene involves migration of the double bond into a trisubstituted position, (XXIII). Dehydrogenation leads to a mixture of

retene and pimanthrene. On the basis of these and other results, BRANDT[32] suggested the structures (XXVIII, R = CH_2) and (XXIII), without their stereochemical implications, for phyllocladene and isophyllocladene, respectively.

These structures were very largely confirmed by a detailed infra-red study of the hydrocarbons and of the nor-ketone[33] which demonstrated the presence, in phyllocladene, of a vinylidene group attached to a five-membered ring, with one methylene group adjacent, one *gem*-dimethyl group and an angular methyl group between two six-membered rings.

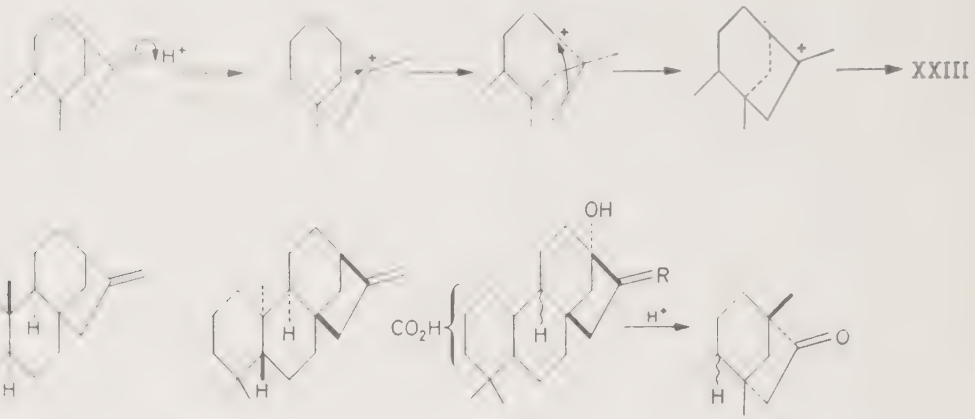
Further degradative experiments[34] have given considerable support to these structures and, in addition, have thrown light on the problem of the stereochemistry of the hydrocarbons. Thus the keto-ester (XXIX), obtained by degradation of isophyllocladene, showed a positive Cotton effect in its ORD curve. This, by the ' Octant rule ', limited its structure to four possibilities[35], only one of which (XXIX) has the ' natural ' stereochemistry at centres 5 and 10. Since rimuene is convertible both into isophyllocladene and an abietadiene (XXVII)[29] of known absolute configuration, it follows that phyllocladene and isophyllocladene must be represented by structures (XXVIII, R = CH_2) and (XXIII), respectively. This has been further confirmed[36a, b] by the degradation of isophyllocladene to the podocarpenone (XXX), identical with that obtained from manool[37].

Mirene

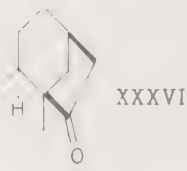
This hydrocarbon, isolated from the essential oil of the New Zealand miro pine (*Podocarpus feruginea*), is chemically very similar to phyllocladene and has an almost identical infra-red spectrum[34].

Isomerization with acetic acid leads to the formation of isophyllocladene, and on this basis, structure (XXXI, R = CH_2) was assigned to mirene[31, 34]. However, this assignment may be criticized on two counts. First, it is difficult to envisage a reasonable mechanism for the transformation (XXXI, R = CH_2 → XXIII), and secondly, the nor-ketone from mirene exhibits a negative Cotton effect, whereas the nor-ketone (XXXI, R = O) would be expected to exhibit a positive Cotton effect[38a]. The ketone (XXXVI), considered as a possible structure for the mirene nor-ketone, has been obtained from phyllocladene, but is not identical with the nor-ketone from the natural product[38a]. The structure (XXXII) has recently been proposed for mirene[38b]. This structure would be expected to lead to a nor-ketone

having a negative Cotton effect, and is readily convertible, by way of carbonium ion rearrangements, to isophyllocladene.



XXXII XXXIII XXXIV XXXV



XXXVI

Kaurene and Steviol

Kaurene, which was earlier known[27] as podocarprene, occurs naturally in both the dextro- and laevorotatory forms. The structure (XXXII) has been proposed[31] for 'kaurene' on biogenetic grounds and on the basis of the argument that such a structure would be more stable than the corresponding *trans-syn-trans* arrangement (mirror image of XXXIII). In fact, models suggest the reverse order of stability, and the recorded positive Cotton effect for the nor-ketone[31] is apparently incompatible with structure (XXXII). More recently, it has been suggested that (−)kaurene is (XXXIII), which is in accord with the optical data for the nor-ketone and for the keto-acid analogous to that (XXIX) obtained from phyllocladene[38b]. This conclusion receives support, so far as the orientation of the five-membered ring is concerned, from the conversion of steviol (XXXIV), by a sequence of reactions which cannot affect the stereochemistry of the molecule at any significant centre, into α-dihydro-(−)-kaurane[10b].

Steviol is the aglycone of the glycoside stevioside isolated from the leaves of the Paraguayan plant *Stevia rebaudiana* Bertoni[39]. It contains a carboxyl, a tertiary hydroxyl and a vinylidene group. On treatment

with acid it isomerizes to isosteviol, which contains a saturated carbonyl function in a five-membered ring. On the basis of these and other results, the partial structures (XXXIV, R = CH_2) and (XXXV) have been advanced[40a] for steviol and isosteviol, respectively. The β-configuration of the five-membered ring in steviol is confirmed by the superimposability of the ORD curves of the nor-ketone (XXXIV; R = O) and of the corresponding ketone from allogibberic acid (see below). Similarly, the ORD curves of isosteviol and gibberic acid are superimposable.

By a sequence of reactions which cannot affect the stereochemistry of the molecule, steviol has been converted into α-dihydro-(−)-kaurane[40b]. It follows, therefore, that (−)-kaurene has a β-five-membered ring, in agreement with the positive Cotton effect of the nor-ketone[31], and the possible structures for this hydrocarbon are therefore limited to three: (XXXI), (XXXIII) and the mirror image of (XXXII).

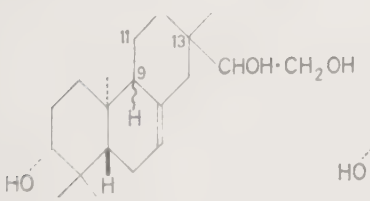
DITERPENOIDS OF 'UNNATURAL' STEREOCHEMISTRY

Recently, terpenoids have been discovered with the 'unnatural' stereochemistry about the A/B-ring-junction, i.e. a 5(β)-hydrogen and a 10(α)-methyl group. Some of the more important diterpenoid examples of this class will be discussed below.

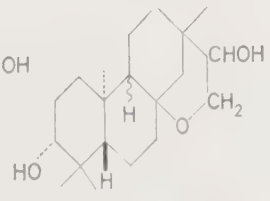
Darutigenol

Darutigine, isolated from *Siegsbeckia orientalis* L., ('Guerit Vite'), has now been investigated in detail, and its structure elucidated[41]. In view of its glycosidic nature, the new name darutigoside is proposed, the aglycone being the diterpenoid triol, darutigenol.

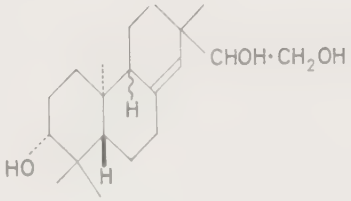
Enzymatic hydrolysis of the glycoside yielded only darutigenol and D-glucose. Acid hydrolysis gave, in addition, the isodarutigenols A, B and C. The proposed structures for darutigenol, isodarutigenol-B and isodarutigenol-C are (XXXVII), (XXXVIII) and (XXXIX), respectively.



XXXVII



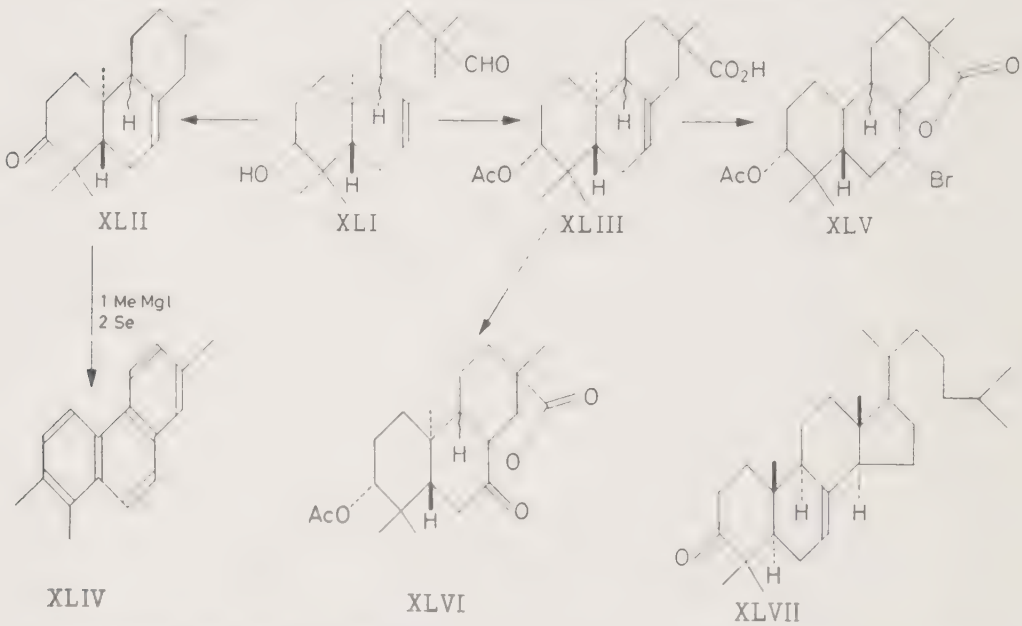
XXXVIII



XXXIX

Darutigenol exhibits no selective absorption in the ultraviolet above 220 mμ and has a strong band in the infra-red at 3,330 cm $^{-1}$. It readily forms a triacetate or benzoate which can be isomerized under normal catalytic hydrogenation conditions to the corresponding triester of isodarutigenol-C. The triacetate readily gives a mono-epoxide with perbenzoic acid, and with osmium tetroxide gives a crystalline penta-ol. It follows, therefore, that darutigenol contains three hydroxyl groups, one double bond and three rings.

Selenium dehydrogenation gave rise to pimanthrene, reminiscent of the behaviour of the pimaric acids, and it was subsequently shown that darutigenol is derived from a stereoisomer of pimarane (III).



XLII XLI XLIII XLV

XLIV XLVI XLVII

Periodate oxidation of darutigenol gave formaldehyde and the aldehyde (XLI), demonstrating the presence of a —CHOH—CH_2OH grouping.

The presence of an equatorial hydroxyl group adjacent to a *gem*-dimethyl group in ring A was diagnosed by the characteristic ring-contraction induced by phosphorus pentachloride. This finding was supported by the sequence (XLI → XLIV), giving the known 1:2:7-trimethylphenanthrene (XLIV).

Treatment of the acetoxy-acid (XLIII) with bromine in chloroform gave a bromo-γ-lactone (XLV). Further, treatment of the acid (XLIII) with an excess of chromic acid gave the keto-γ-lactone (XLVI). This latter reaction is reminiscent of the behaviour of oleanolic acid. It follows from the formation of a γ-lactone in these

reactions that the double bond of (XLIII) is $\beta\gamma$- or $\gamma\delta$- to the carboxyl group. The former arrangement can be excluded because the acid (XLIII) does not readily lose carbon dioxide. Of the remaining positions for the double bond, $\Delta^{9(11)}$- is eliminated by the formation of a γ- rather than a δ-lactone, and the Δ^{8}- isomer fails to explain the formation of the keto-γ-lactone (XLVI). It follows, therefore, that the double bond of darutigenol is in the Δ^{7}-position. This finding was supported by the resistance of the compound to hydrogenation, which is typical of Δ^{7}-steroids.

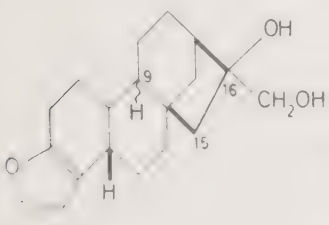
The molecular rotation changes accompanying the transformations —OH → —OAc and —OH → —OBz in darutigenol derivatives such as (XLI) suggested the 'unnatural' stereochemistry at centres 5 and 10. This was confirmed by examination of the ORD curve of the ketone (XLII), which exhibited a Cotton effect in the opposite sense from that of the triterpenoid ketone (XLVII).

Hence darutigenol can be represented by the structure (XXXVII), the stereochemistry in the side chain and at centres 9 and 13 being undefined.

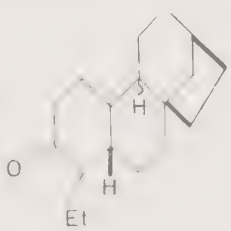
Cafestol and Kahweol

The structure of these coffee constituents, uncertain at the time of the last review[1], has now been almost completely elucidated.

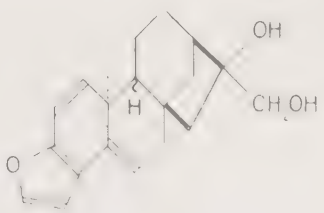
Cafestol was degraded[35, 42] to the ketone (XLIX). Studies on the bromination and reduction of this ketone, and comparison with the behaviour of similar ketones related to friedelin and the normal triterpenes, located the angular methyl group unambiguously at $C_{(10)}$. The ORD curve required that cafestol have the 'unnatural' stereochemistry at centres 5 and 10. The β-orientation of the cyclopentane ring was established by the correspondence[35] between the ORD curves of the $C_{(16)}$-norketone derived from cafestol and of the phyllocladene norketone (XXVIII, R = O). Accordingly, cafestol can be represented by the structure (XLVIII), in which the stereochemistry at centres 9 and 16 is undefined.



XLVIII



XLIX



L

On the basis of this structure for cafestol, its companion kahweol[43] can only be represented[35] by structure (L).

Columbin

This bitter principle of the Colombo root (*Jatrorrhiza palmata* Miers) had been assigned structure (LI), without its stereochemical implications, at the time of the last review[1]. More recently, the stereochemistry of columbin has been partially elucidated[44].

Columbin can be degraded to the keto-acid (LIII), the ORD curve of which is very similar to that of the simple decalone of known absolute configuration (LIV). It follows, therefore, that the 5-methyl group of (LIII), and hence of columbin itself, is α-oriented. The A/B-ring-junction cannot be said to be *trans* on this evidence, but this is very likely on biogenetic grounds.

The biogenesis of columbin, from a hypothetical precursor of the general type (LII), is reminiscent of the biogenesis of friedelin in which an all-axial migration is presumed to occur. If columbin is formed by a similar mechanism, then the 9-methyl group must also be α-oriented.

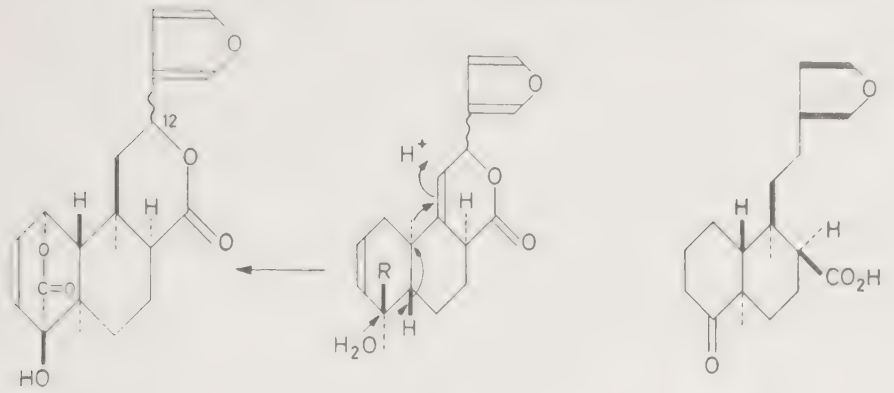
The resistance of the unsaturated lactone ring of columbin to hydrolysis suggested that it was *cis*- to the $C_{(5)}$-methyl group. Hence columbin may be represented as (LI), in which the stereochemistry at $C_{(12)}$ is undefined.

If these arguments are valid, then the hypothetical precursor (LII) of columbin must have the 'unnatural' stereochemistry[44] at centres 5 and 10.

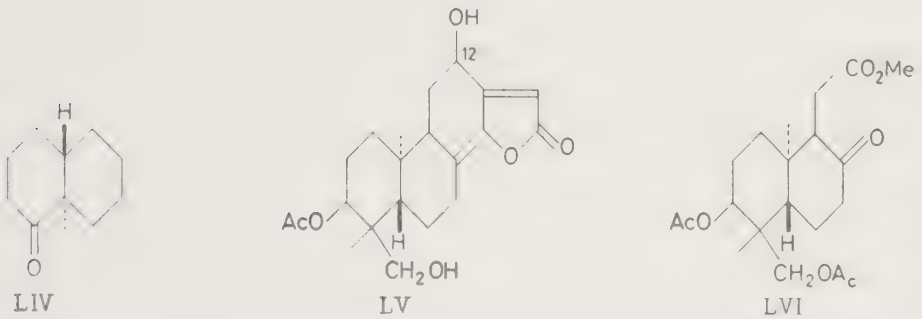
Andrographolide

The previous investigations on this diterpenoid lactone (Cava *et al.*[45]) have led to a determination of the main structural points. Ozonolysis of the triacetate gave the keto-ester (LVI), the ORD curve of which revealed that andrographolide had the 'unnatural' stereochemistry at centres 5 and 10 and could therefore be represented by structure (LV), with the stereochemistry at centres 3, 4, and 12 undefined.

Another example of this class is eperuic acid (LXVI; see p. 111) which is epimeric with labd-8(20)-enoic acid at all asymmetric centres except $C_{(9)}$.



LI LII LIII



LIV LV LVI

MANOOL AND RELATED DITERPENES

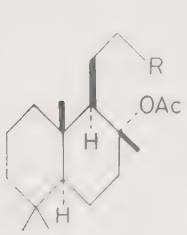
Sclareol, Manool and Manoyl Oxide

The last remaining problem in connection with the structure of these diterpenoids, the configuration of $C_{(13)}$, has recently been solved in the following manner.

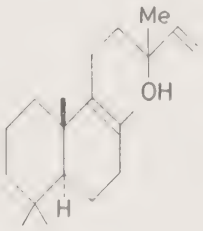
In the course of a synthesis of sclareol and its 13-epimer[46], the ketone (LVII, $R = -CO{\cdot}CH_3$) was ethynylated to give the epimeric ethynyl carbinols (LVII, $R = -COH{\cdot}C{\equiv}CH$ | Me), one of which was intramolecularly hydrogen-bonded. A study of models (LX) led to the conclusion that such hydrogen-bonding would only be possible when the slimmer ethynyl group was β-oriented (LX; $R' = C{\equiv}CH$, $R'' = Me$), because of non-bonded interactions between the groups enclosed in dotted lines.

Reduction of the non-bonded isomer with lithium aluminium hydride gave sclareol, which therefore has the 13(R)-configuration[47] (LIX $R = \langle^{OH}_{Me}$).

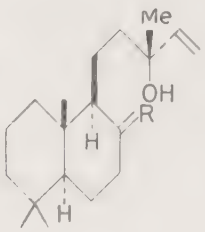
This conclusion, which was in opposition to BÜCHI's previous tentative assignment[48], was supported by a careful analysis of molecular rotation data for several derivatives of manool and R(+) linalool (LXI)[49].



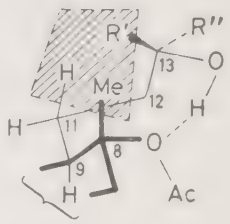
LVII



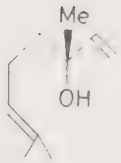
LVIII



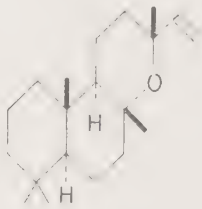
LIX



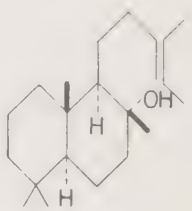
LX



LXI



LXII



LXIII

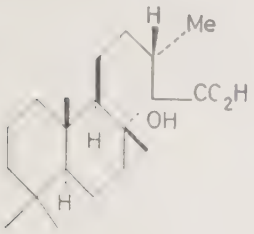
Since manool has been obtained from sclareol[48, 50], it follows that manool is (LIX, R = CH_2).

The recent claim that manoyl oxide is produced on dehydration of sclareol[50] has been shown to be only partially correct[51]. The main product is, in fact, 13-epimanoyl oxide. Hydrogenolysis of manoyl oxide, and of 13-epimanoyl oxide, furnished the same 8-(α)-hydroxy-labdene (LXIII), and a study of the electron-impact induced fission of manoyl oxide and 13-epimanoyl oxide suggested that in the former the arrangement of the axial groups was the more congested. Accordingly, a 13-(β)-methyl structure was assigned to manoyl oxide, which thus has the structure (LXII), on the assumption that ring C was in the normal chair form.

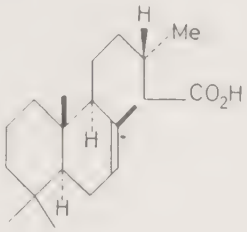
Labdanolic, Cativic and Eperuic Acids

Labdanolic ester and its $C_{(13)}$-epimer have been synthesized from sclareol[52]. From a consideration of the molecular rotations of these compounds, labdanolic acid was assigned the 13(S)-configuration (LXIV). This result has been confirmed by an independent synthesis of the two acids and a study of their infra-red spectra[46]. Structures

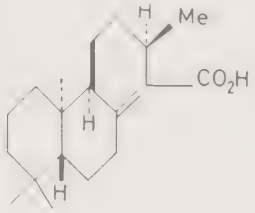
(LXV) and (LXVI) can now be assigned to cativic and eperuic acids, respectively, from a knowledge of their relationship to labdanolic acid.



LXIV



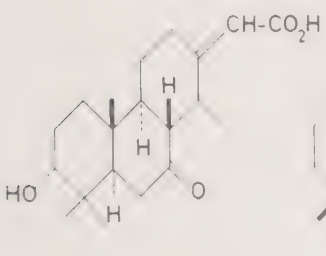
LXV



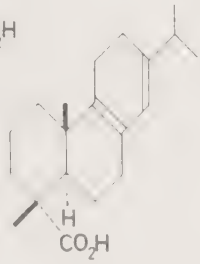
LXVI

MISCELLANEOUS DITERPENOIDS

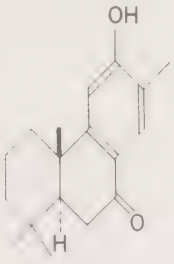
While for reasons of space the details cannot be given, it may be noted that structures have been assigned to the following compounds: cassaic acid[53] (LXVII), palustric acid[54] (LXVIII), nimbiol[55] (LXIX) and hinokiol[56] (LXX). The structure of gibberellic acid is still not certain, but there now seems good evidence[57] in favour of the β-oriented lactone ring (LXXI). Xanthoperol (LXXII) has been shown to have a *cis*-A/B-junction[58], and the absolute stereochemistry of phytol has been determined; ORD measurements[59] and synthesis[60] show that it has the configuration 7(R)-11(R)-*trans*- (LXXIII).



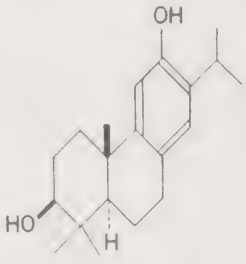
LXVII



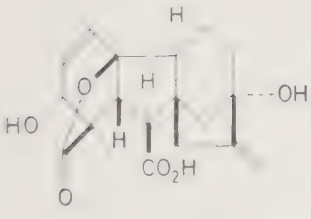
LXVIII



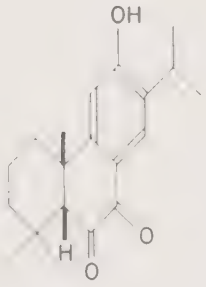
LXIX



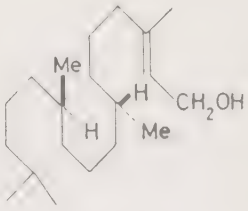
LXX



LXXI



LXXII

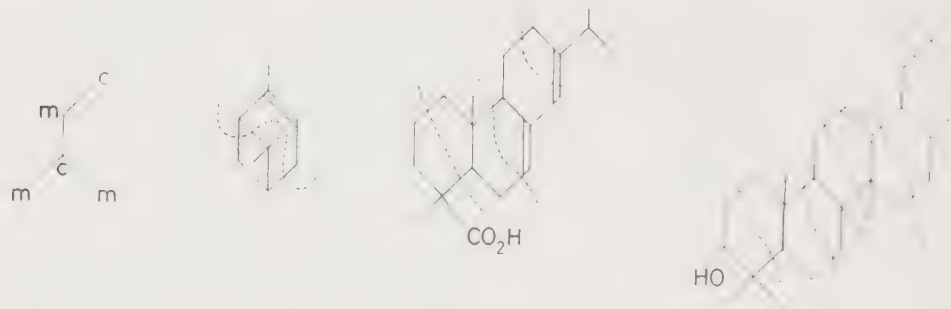


LXXIII

TERPENE BIOGENESIS

In the remainder of this chapter we review the present state of knowledge of the processes of terpene biosynthesis. The discussion of this topic will be simplified if we anticipate the conclusion that steroids, e.g. cholesterol (XCI), are members of the same class derived from the triterpene squalene (LXXXVIII).

In the 100 years which have elapsed since the word isoprene was coined[61] the structures of a very large number of terpenes have been elucidated, and from consideration of this wealth of data there gradually emerged the realization that these substances are constructed on a definite architectural plan. This plan is crystallized in the *Isoprene rule* which states that the skeletons of these natural products are constructed by the linking of two or more isoprene or isopentane units (LXXIV) (see *Figure 1*).



LXXIV — α - Pinene — Abietic Acid — β Amyrin

(m = methyl carbon of acetic acid)
(c = carboxyl carbon of acetic acid)

Figure 1

This unity of structure, based upon a common isopentane building block, implies an underlying unity in the biochemical mechanisms responsible for the synthesis of these substances. Recently, Ruzicka[62], one of the great pioneers in this field, summarized his views on the complex interrelations in this group and proposed a generalization called the 'Biogenetic Isoprene Rule', according to which terpenoids are formed by a preliminary telomerization of isopentane (C_5) units into a few aliphatic substances such as geraniol (C_{10}) (LXXXIII, H instead of PP; p. 116), farnesol (C_{15}) (LXXXIV, H instead of PP), geranyl-geraniol (C_{20}, LXXXV) and squalene (C_{30}, LXXXVIII; p. 121) which subsequently cyclize and (where appropriate) rearrange by accepted mechanisms to give the individual members of the classes of mono-, sesqui-, di-, and tri-terpenes (and steroids), respectively. This statement has proved of great value as a guiding principle in the eluci-

dation of the structures of complex triterpenes, and it proposes a view of terpene biogenesis which has received a very considerable measure of support in recent investigations.

Consideration of the biosynthesis of terpenoids according to this view falls under two headings. First, there is the problem of the mechanism of the self-condensation of small molecules such as acetate into the active C_5 units and the polymerization of these C_5 units to the aliphatic precursors (geraniol, squalene, etc.) and secondly, there is the question of the cyclization, rearrangement and tailoring of these precursors on their way to the final products.

Acetate as Precursor

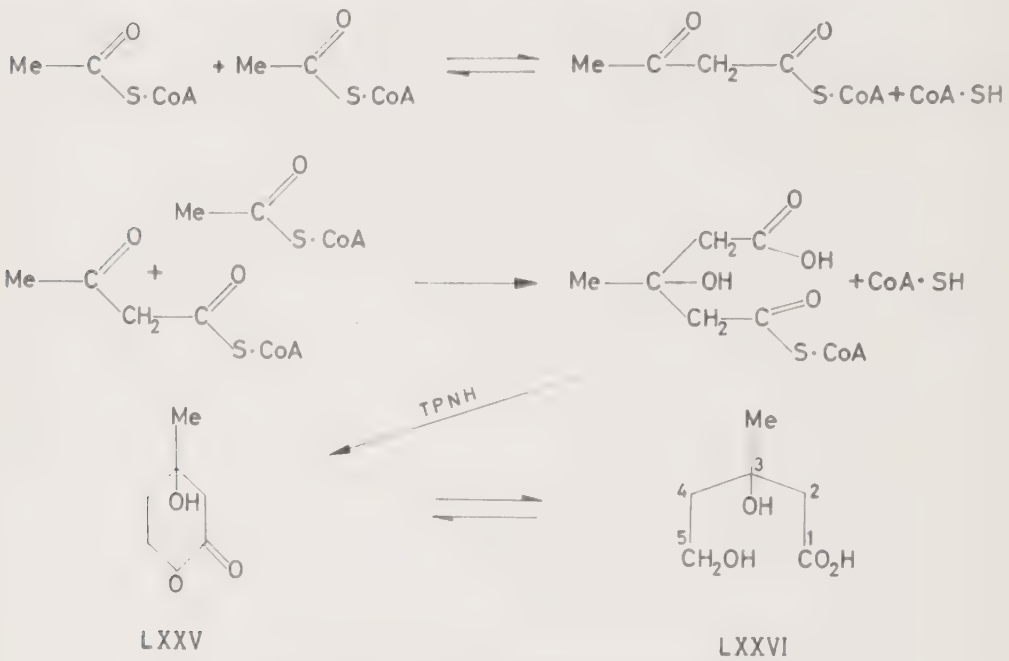
The role of acetate as a precursor of terpenoids, indicated by the early work[63,64] on sterols, has become firmly established by the subsequent results stemming from the use of acetate labelled with ^{13}C or ^{14}C. By this means it has been shown that acetic acid is a carbon source for the biosynthesis of all steroids and terpenoids so far investigated, e.g. geraniol[65], rubber[66], β-carotene[67], squalene[68], soyasapogenol-A[69], rosenonolactone[70], eburicoic acid[71], cholesterol[72], gibberellic acid[73], with the exception that certain 'extra' carbon atoms, e.g. C_{28} in eburicoic acid (C) and C_{28} in ergosterol, appear[74] to be derived from formate.

This work has shown that both carbon atoms of acetic acid are incorporated into biosynthesized terpenoids. Subsequent work on the degradation of labelled terpenoids derived from isotopically labelled acetic acid has shown that the two carbon atoms of acetic acid to a very large extent preserve their identity and appear at specific points in these terpenoid skeletons. Cholesterol has been investigated in more detail (reviewed[75]) than any other terpenoid and, largely as a result of the masterly investigations of Cornforth and Popják[76,77], the origin of all the carbon atoms in cholesterol which had been derived from acetate has been shown to be as in (XCI; p. 121). The distribution of the isotopic carbon atoms in the side chain[78] and in ring A[77] reveals the presence of isopentane units labelled as in (LXXIV). An examination[79] of the triterpene squalene (LXXXVIII) reveals that its isopentane units are labelled in the same fashion.

The nature of this isopentane unit and its mode of synthesis from acetate posed problems of great difficulty (see Bloch[75b]) which were not resolved until the isolation[80] of β-hydroxy-β-methyl-δ-valerolactone (LXXV), the lactone of mevalonic acid (MVA)

(LXXVI) and the demonstration[81] that this substance is converted virtually quantitatively into cholesterol in rat liver homogenates and that it is a much better source than acetate and other previously postulated intermediates, i.e. that it is probably a direct precursor.

MVA is derived from acetate in the form of its coenzyme-A (CoA) derivative by a sequence of Claisen-like condensations[82] (*Figure 2*).



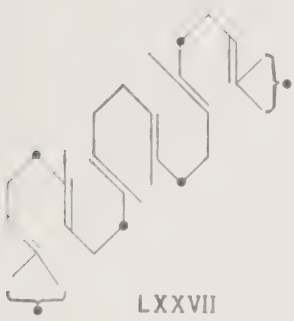
Reduced form of TPN or triphospho-pyridine nucleotide

Figure 2

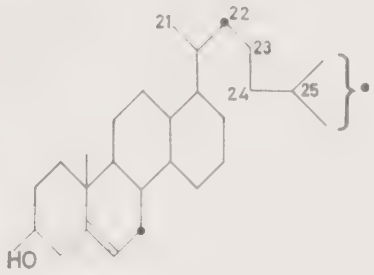
It is known[81b] that MVA decarboxylates on its way to cholesterol; such decarboxylation of a molecule of MVA derived from acetate units as in *Figure 2* will clearly lead to a C_5 unit with the required distribution of carbon atoms (LXXIV). The formation of polyisoprenoids is then to be visualized in terms of condensation of C_2 of one MVA molecule with C_5 of another, and so on.

The key position occupied by MVA in terpene biogenesis is now firmly established. When 2-^{14}C-MVA is transformed into squalene, all the radioactivity is found[83] in the dotted carbon atoms (LXXVII). When the same substance is converted into cholesterol[84] radioactivity was found in the atoms marked in (LXXVIII) but not in positions 20, 21, 23, 24 and 25. Other work has shown that 2-^{14}C-MVA is incorporated into soyasapogenol-A (CI) (ARIGONI[69]), rosenonolactone[70] (CV), gibberellic acid[73] (CVI), mycelianamide and mycophenolic acid[85] in such manner as to confirm the view that these

products arise by decarboxylation of MVA to a C_5 unit which undergoes the transformations postulated by the biogenetic isoprene rule.



LXXVII



LXXVIII

The precise nature of this C_5 unit and the manner in which it is derived from MVA have very recently become clear as a result of the splendid investigations of Lynen and Bloch and their co-workers. The present state of knowledge of this subject is represented diagrammatically in *Figure 3*.

This breakdown of the overall process of terpene synthesis was initiated by observations that the transformation of MVA into terpenoids by cell extracts was dependent upon the presence of ATP, Mn^{++} or Mg^{++} as well as reduced pyridine nucleotides. This led to a search for phosphorylated intermediates which had far reaching consequences. The evidence on which this scheme rests is perhaps best discussed under the headings of the particular intermediates.

Mevalonic Acid-5-phosphate (LXXIX) *(PMVA) and -5-pyrophosphate* (LXXX)

The first step in the biosynthesis is the phosphorylation of MVA by ATP. In reactions catalysed by yeast or liver enzyme fractions[86,87] PMVA can be isolated. Since it is formed both from 1-^{14}C- and 2-^{14}C-MVA, it must contain a carboxyl group, and experiments involving AT^{32}P show that it contains one phosphate group per C_6 unit. The stability of the compound precludes an acyl phosphate structure and strongly suggests that the phosphate grouping is present as an ester, and linked to position 5, an assignment proved by synthesis in Lynen's laboratory. This compound is efficiently converted into squalene and cholesterol and appears to be the first product of the overall transformation.

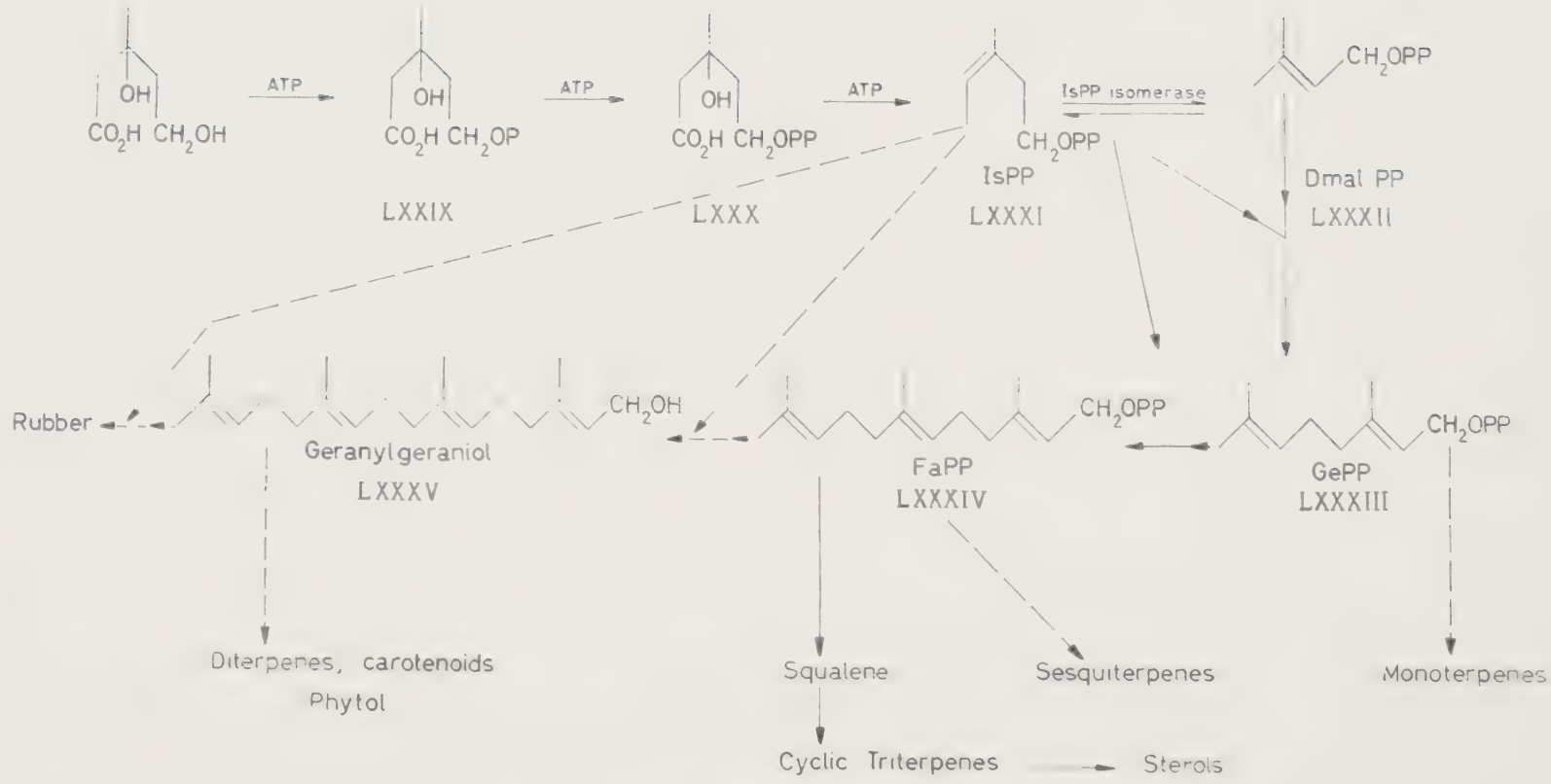


Figure 3

Full lines show known reactions; dotted lines indicate postulated reactions, as yet unproved.

Abbreviations: Isopentenyl pyrophosphate, IsPP; dimethyl allyl pyrophosphate, DmalPP; geranyl pyrophosphate, GePP; farnesyl pyrophosphate, FaPP; adenosine triphosphate, ATP; phosphate, P; pyrophosphate, PP.

The observation[88] that ATP is still required for the further metabolism of PMVA suggests the existence of further phosphorylations, and CHAYKIN *et al.*[89] demonstrated the formation from PMVA of a compound containing two phosphate groupings which retained the carboxyl group of MVA and was shown by hydrolysis back to PMVA to be an MVA diphosphate. Stability studies suggested the presence of a pyrophosphate linkage, and the compound was therefore assumed to be MVA-pyrophosphate. CHAYKIN *et al.* also showed that it was a precursor of isopentenyl pyrophosphate and of squalene.

Isopentenyl Pyrophosphate (*IsPP*) (LXXXI)

Preliminary investigations into the prolonged action of ATP and yeast extracts on PMVA indicated the successive formation of MVA-pyrophosphate and of a new compound lacking the carboxyl group of MVA. It was shown[89] that this latter substance contained another phosphate group in addition to the original phosphate group of PMVA and that the action of phosphatase led to the formation of isopentenol identical with synthetic material. LYNEN *et al.*[88] obtained similar results and showed that synthetic IsPP is identical with this biochemical transformation product of PMVA.

The formation of IsPP from MVA-pyrophosphate involves decarboxylation and dehydration, and although the process is ATP-dependent[89], no extra phosphate group is introduced. Furthermore, the decarboxylation and dehydration are concerted, for during the synthesis of squalene from MVA in D_2O (and T_2O), no hydrogen is transferred from the medium to an intra-chain carbon atom of the squalene chain[90] (see p. 119.) One must therefore postulate:

2-^{14}C-PMVA is shown[88a] to lead to IsPP labelled as shown above.

There can now be little doubt but that IsPP and its successor DmaPP (LXXXII) are the 'active isoprenes' which polymerize to the terpenoids, for 1-^{14}C-IsPP has been enzymatically converted[88a] into squalene, cholesterol, rubber, FaPP and GePP[91]. That the active isoprene might be a derivative of isopentenol was first predicted by BLOCH and his co-workers[92].

Dimethylallyl Pyrophosphate (*DmalPP*) (LXXXII)

In experiments using a crude yeast extract with no TPNH added, MVA and PMVA were converted[88a] not into squalene but into a phosphorylated intermediate (farnesyl pyrophosphate) characterized by its ready hydrolysis to pyrophosphate by acid. An assay based on this lability has revealed[93] the presence of an enzyme, isopentenol pyrophosphate isomerase, which catalyses the isomerization of IsPP to DmalPP. In the presence of SH-poisons such as iodoacetamide or chloromercuribenzoate, this enzyme is inhibited and IsPP accumulates.

The structure of DmalPP, shown[93] by its enzymatic hydrolysis to pyrophosphate and dimethylallyl alcohol, was confirmed by synthesis[91].

Geranyl Pyrophosphate (*GePP*) (LXXXIII) *and Farnesyl Pyrophosphate* (*FaPP*) (LXXXIV)

The conversion of MVA and PMVA into squalene by yeast extracts requires TPNH, ATP and Mg^{++}. If the TPNH (essential for the reductive dimerization of farnesyl residues) is omitted, then an acid-labile allylic pyrophosphate accumulates which was shown[88a] by chemical and enzymatic hydrolysis to be FaPP. The same reaction can be demonstrated with IsPP, except that no ATP is required.

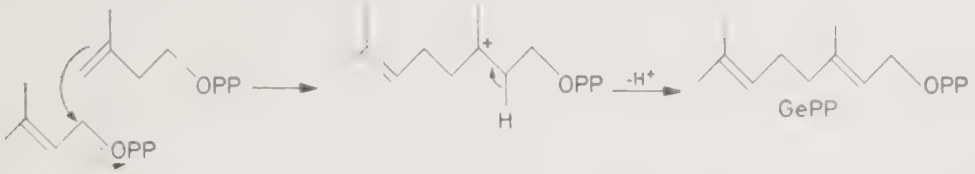
The biosynthesis of FaPP is not a simple self-condensation of DmalPP, because synthesizing systems provided with DmalPP fail to produce FaPP in the absence of IsPP and IsPP isomerase[91,94]. Neither is the reaction a self-condensation of IsPP, for yeast extracts in which the IsPP isomerase has been poisoned with iodoacetamide and which will convert a mixture of IsPP and DmalPP into squalene, fail to do so in the absence of DmalPP[91]. It follows that IsPP and DmalPP must both be present if polyisoprenoids are to be formed.

The enzyme responsible for linking of the C_5 units (farnesyl pyrophosphate synthetase) has now been purified twentyfold, and with this enriched preparation it has been shown[91] that the synthesis of FaPP involves a primary reaction between IsPP and DmalPP to give GePP which then condenses with the second molecule of IsPP to give FaPP. The further condensation of FaPP with IsPP to give geranylgeraniol has not yet been demonstrated experimentally.

Mechanism of the Conversion of IsPP and DmalPP into Squalene

Lynen[88a,91] and Bloch[90] hav postulateed that the formation of FaPP is a C-C-alkylation in which an allylic carbonium ion, derived by

heterolysis of DmalPP, alkylates the reactive double bond of IsPP with loss of a proton to give GePP:



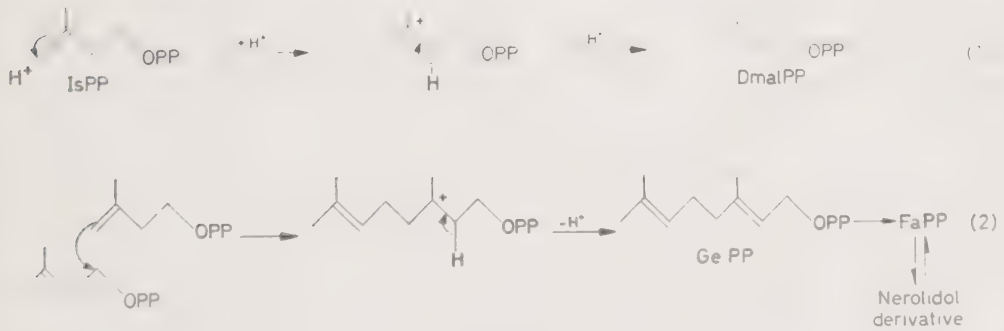
The GePP so formed is itself an allylic pyrophosphate and could thus similarly alkylate another molecule of IsPP to give FaPP. The intervention of carbonium ions has not been proved, and it might well be that the proton elimination is concerted with the alkylation process.

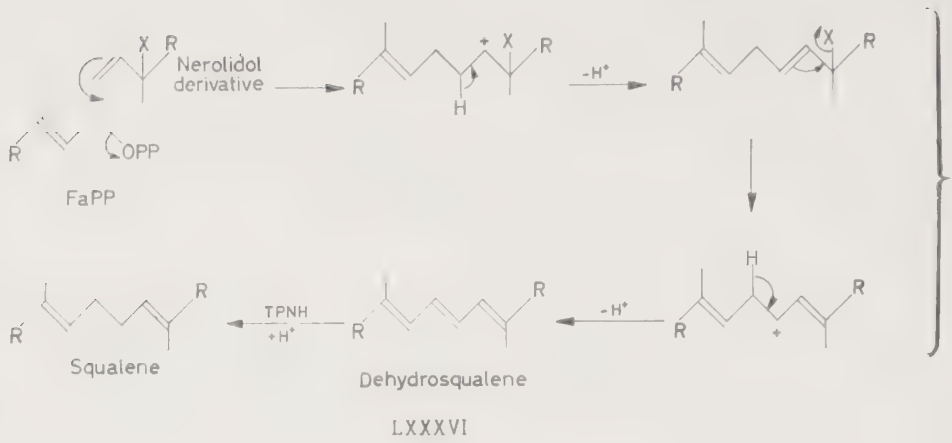
Any acceptable mechanism for these transformations must accommodate the following facts[90]:

(*i*) That during the condensation of 6 molecules of 5-D_2-MVA to give one molecule of squalene, out of the 12 atoms of deuterium which might possibly have been incorporated, only 10 were found to be present in the final product. The 2 missing deuterium atoms were lost from the 2 central CH_2 groups of squalene.

(*ii*) That the synthesis of squalene from MVA in heavy water leads to an uptake of about 4 deuterium atoms from the solvent. Of these, 2 were found on the terminal isopropyl groups and 2 were located on the 2 central carbon atoms of squalene.

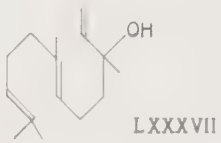
With this in mind, and stimulated by the discovery[95] that an acid-labile derivative (presumably pyrophosphate) of nerolidol (LXXXVII; an allylic tautomer of farnesol) accompanies the FaPP formed in a liver system from MVA, CORNFORTH and POPJÁK[96] have proposed the following detailed mechanism for the biogenesis of squalene, with the reservation that many of the electron shifts may be concerted:





(3)

LXXXVI



LXXXVII

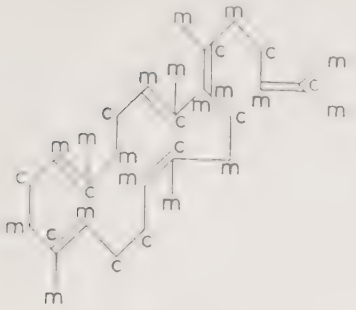
This mechanism provides an explanation of the facts (*i*) and (*ii*), for processes (1) and (2), which are essentially the same as those previously suggested by LYNEN[88a] and BLOCH[90], require the introduction into the terminal isopropyl group of a hydrogen atom not originally contained in MVA. Process (3), the reaction between FaPP and a nerolidol derivative, gives rise to squalene *via* dehydrosqualene (LXXXVI), and this requires that two protons originally bound to C_5 of MVA be eliminated and subsequently replaced by two others.

Squalene as a Precursor of Sterols

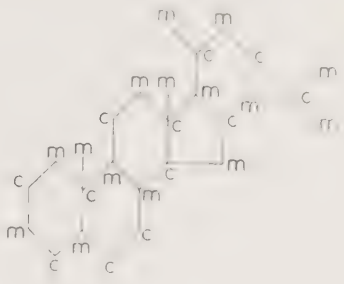
Since the implications of the biogenetic isoprene rule have been subjected to a detailed scrutiny only with the transformation products of squalene, i.e. cholesterol, lanosterol and the triterpenes, this aspect of the subject is best discussed first. The results so obtained can then be extrapolated to the less well known regions of terpene biogenesis.

The earliest suggestions[97] that squalene and the sterols might be related biogenetically were given a detailed form by ROBINSON[98], who envisaged a cyclization and demethylation of squalene as in (LXXXVIIIa). This implies that a sterol molecule biosynthesized from acetate should have the isotope distribution shown in (LXXXIX).

Subsequently, when the biosynthesis of sterols had become an experimental area, the role of squalene as a sterol precursor was put on a firm basis by the demonstration[99] of an efficient conversion of the one



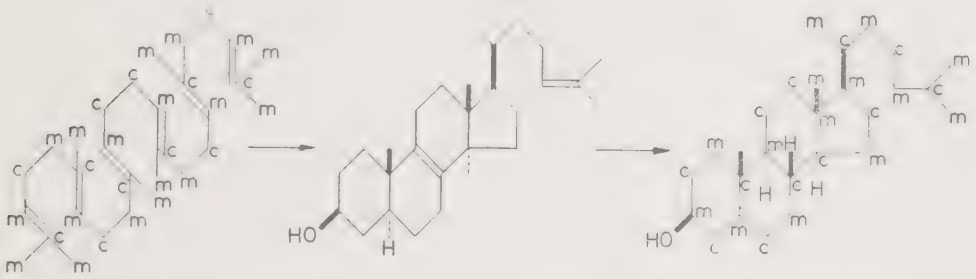
LXXXVIIIa



LXXXIX

into the other. More recently it has been shown[100] that sterol synthesizing systems, operated under anaerobic conditions, accumulate squalene.

The folding of the squalene molecule advanced by Robinson is not unique, and Dauben *et al.*[101] and Woodward and Bloch[102] independently suggested that cholesterol might be derived by cyclization and rearrangement of the methyl groups from a molecule of squalene folded as in (LXXXVIIIb).



LXXXVIIIb XC XCI

Figure 4

These two modes of cyclization predict different origins for the carbon atoms at positions 7, 8, 12 and 13 in cholesterol derived from acetate. All degradative studies, and in particular a remarkable degradation and isotopic analysis[76,77] of the entire cholesterol skeleton, are in complete accord with the requirements of the biosynthetic scheme of *Figure 4*.

That lanosterol may be a real rather than a hypothetical intermediate receives support from the biosynthesis of lanosterol from squalene and its subsequent conversion into cholesterol[103]. The evidence on this point is reviewed by Bloch[75b].

Mechanisms of Squalene Cyclization

The implication of squalene and lanosterol as intermediates in the biosynthesis of cholesterol led RUZICKA *et al.* to propound[62] a general scheme, the biogenetic isoprene rule (see p. 112), for the biogenesis of terpenoids and sterols. In 1955, an extension of the scheme was advanced[104] which, taking into account the stereochemical aspects of the cyclization of the aliphatic precursors, permits an *a priori* derivation not only of the structures but also of the configurations of terpenes, in particular of the triterpenes.

With respect to squalene the following explicit assumptions are made:

(*i*) That squalene, known[105] to possess the all-*trans* configuration at the double bonds, cyclizes *via* a folded form with a definite pattern of chair and boat conformations.

(*ii*) That the subsequent addition, elimination and rearrangement reactions responsible for the formation of the triterpene skeletons proceed by stereospecific *trans*-planar mechanisms.

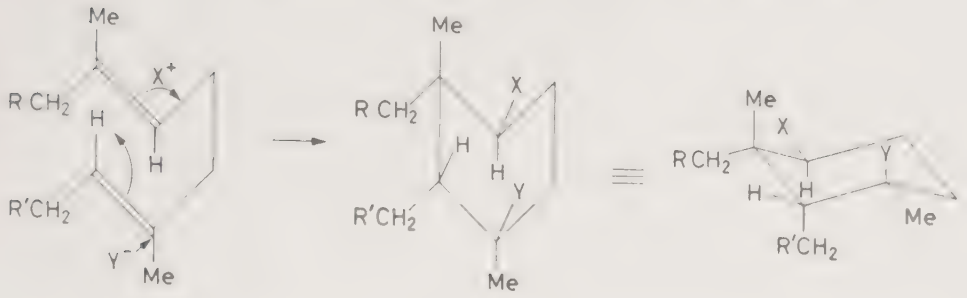
(*iii*) That the overall process is concerted, i.e. that no intermediate carbonium ions are produced.

The impact of these hypotheses is best first examined in a simple system[106]. The cyclization by a concerted anti-planar mechanism of the polyisoprenoid (XCII) folded in the chair conformation leads to a system (XCIII) in which all four groups R CH_2, R′CH_2, X and Y are equatorial and *trans*. This will give a *trans-anti-trans* arrangement of rings in a polynuclear system.

XCII XCIII

The corresponding boat conformation (XCIV) will give the cyclohexane (XCV) equivalent to a *trans-syn-trans* locking of rings in a polynuclear system.

Seen in this light, the biogenesis of lanosterol proceeds as in *Figure 5* by a *trans*-planar cyclization triggered by a cationoid entity, written formally as OH^+, of a squalene molecule folded in the chair-boat-chair-boat



conformation (XCVI). This gives an intermediate ion (XCVII ≡ XCVIII) from which lanosterol (XCIX) is derived by concerted *trans*-planar 1:2-shifts of hydrogen and methyl groups.

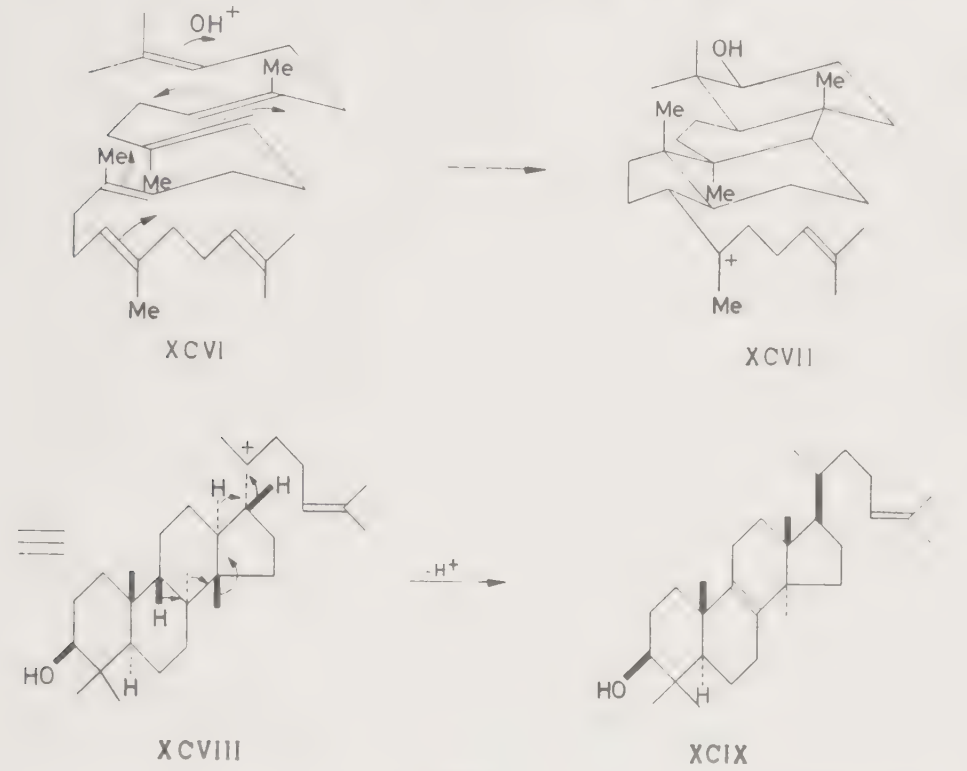


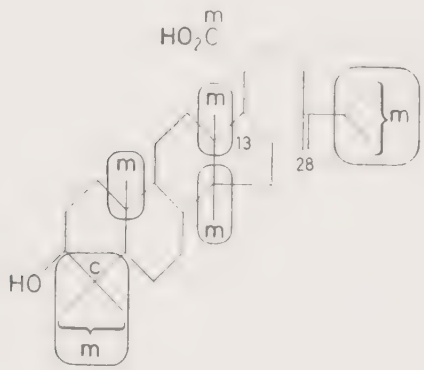
Figure 5

In support of this formulation TCHEN and BLOCH[103a, 107] have shown that the conversion of squalene into lanosterol by liver homogenates is concerted, since cyclization performed in D_2O gave virtually no deuterium in the final product: the $C_{(3)}$ hydroxyl function derives from atmospheric oxygen, not water. Finally, it has been shown[108] that the methyl migrations (XCVIII → XCIX) proceed by two 1:2-shifts

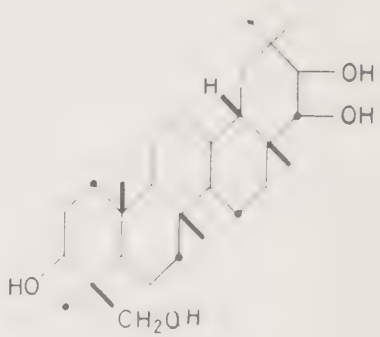
rather than by a single 1:3-migration of the $C_{(8)}$-methyl to $C_{(13)}$. The nature of the further stages in the transformation of lanosterol into cholesterol and other steroids, though they are rapidly becoming clear, will not be discussed here.

By mechanisms similar to those exemplified in *Figure 5*, squalene, cyclizing in other conformational modes, can be shown, in principle, to give rise to all the other tetra- and pentacyclic triterpenes. Since this is a matter which has been discussed lucidly and at length elsewhere[109], we shall pass on immediately to other experimental results obtained in this area, commenting only that the simplicity, elegance and power of this extension of the biogenetic isoprene rule, coupled with the rapidly increasing experimental support, compel belief in its validity.

Dauben and his co-workers[71] determined the origin of some of the carbon atoms in eburicoic acid which had been biosynthesized from labelled acetic acid, with the results shown in (C). This distribution is in excellent agreement with the hypothesis that squalene (LXXXVIII) is a precursor. Furthermore, of the 5 moles of acetic acid (derived from the ringed regions of (C) obtained by a Kuhn-Roth oxidation of



C



CI

eburicoic acid) the carboxyl groups of only 4 originated in the carboxyl of acetic acid; on the squalene hypothesis, $C_{(13)}$ is derived from the methyl group of acetate (see *Figure 4*).

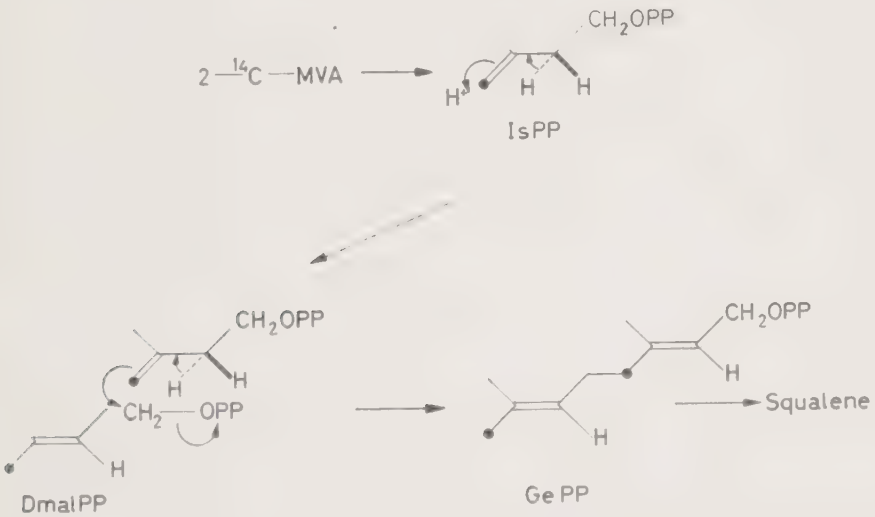
The biogenetic isoprene rule predicts that soyasapogenol-A, which had been biosynthesized from 2-^{14}C-MVA *via* squalene, should have 6 radioactive carbon atoms located at the indicated positions in (CI). A Kuhn-Roth oxidation of this substance gave acetic acid labelled almost exclusively in the methyl group and to an extent nearly equal to that calculated for two labelled methyl groups per molecule[69]. The

CH_2OH group stationed at $C_{(4)}$, being found to be inactive, must therefore derive from the $C_{(3)}$-methyl group of MVA. This implies that if squalene is in fact a precursor of soyasapogenol-A, the cyclization occurs with a chair-folding of the potential ring A (CII), and that this labelled carbon atom has a *cis*-relationship with respect to the hydrogen atom of the first double bond. A similar relationship has also been demonstrated[83, 110] for the internal double bonds of squalene. This, in

CII

Soyasapogenol-A

turn, implies that, during the conversion of MVA into squalene, both $C_{(2)}$ and the methyl group of MVA remain distinct, so that both the isomerization of IsPP to DmalPP and the condensation of IsPP with DmalPP would appear to be stereospecific:



Biogenesis of Diterpenes

According to the biogenetic isoprene rule, it is geranylgeraniol or a related system such as geranyllinalool (CIII) which is the precursor of diterpenes, and from which the latter substances are derived by cyclization initiated by a cationoid entity, usually a proton, followed

where appropriate by skeletal rearrangement, oxidation, etc. *Figure 6* illustrates some of the proposals which have been made.

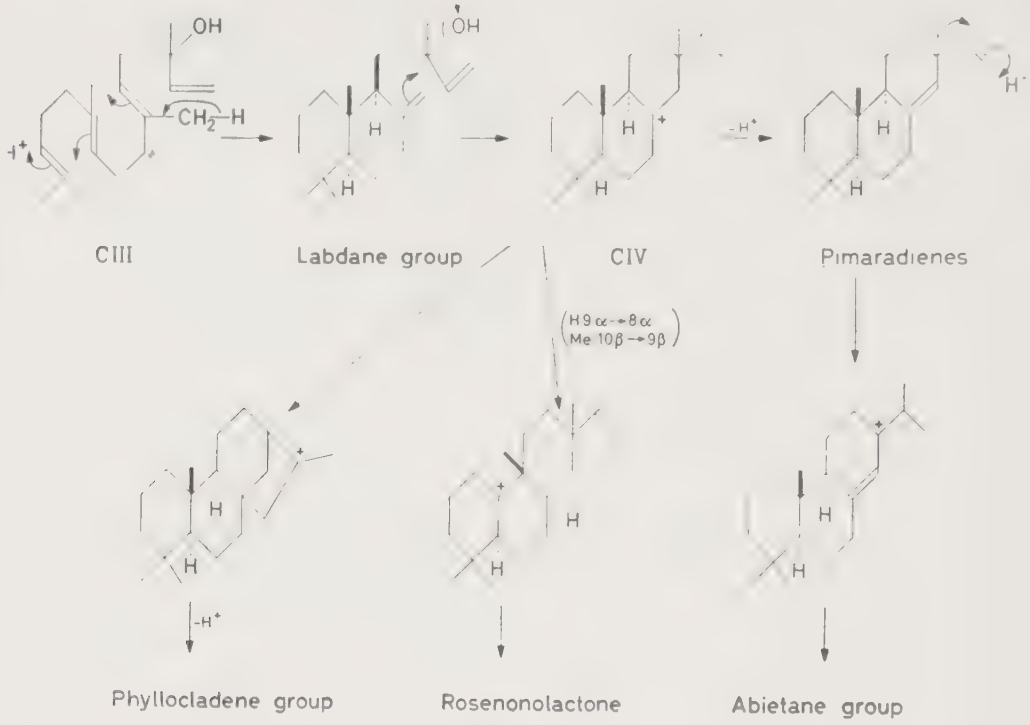
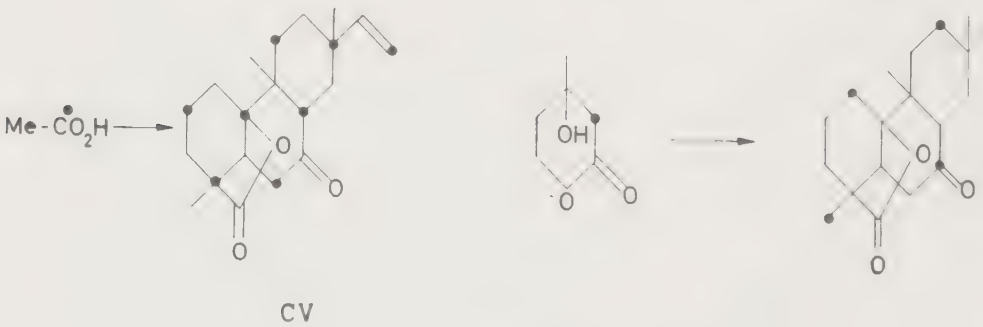


Figure 6

Such little experimental evidence as exists at present is in accord with the predictions of such schemes. In particular the biogenetic isoprene rule predicts (see *Figure 6*) that rosenonolactone (CV) derived from 2-^{14}C-MVA and 1-^{14}C-acetic acid will have the isotope distributions of *Figure 7*.



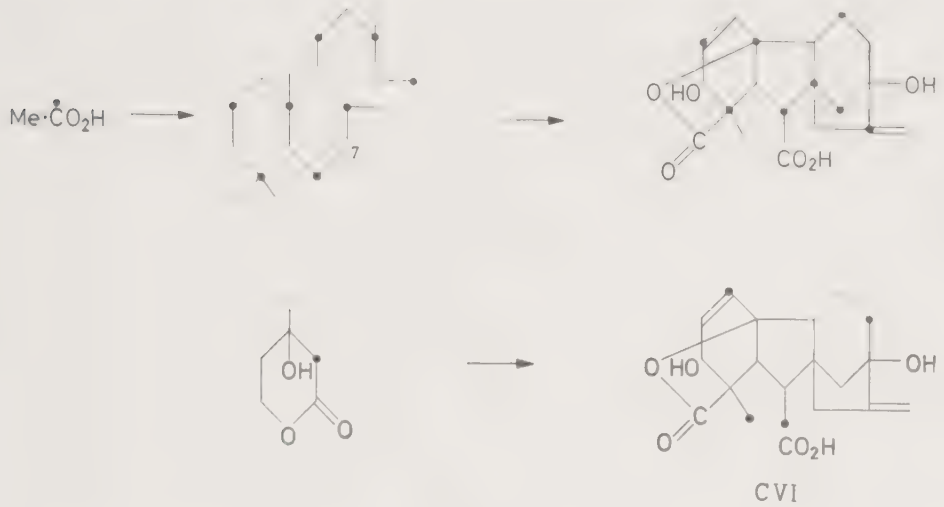
CV

Figure 7

The degradative data obtained by BIRCH[111] and ARIGONI[70, 112] confirm this expected distribution of isotope and, moreover, reveal that

as in the case of soyasapogenol-A, $C_{(2)}$ and the methyl group at $C_{(3)}$ in MVA remain distinct during the biosynthetic process.

An examination[73, 111] of gibberellic acid (CVI) has given results in quantitative agreement with a distribution of isotope as in *Figure 8*.



CVI

Figure 8

The biogenesis of this compound thus probably proceeds by a variant of the scheme of *Figure 6* involving an oxidative loss of the $C_{(10)}$-methyl group of a diterpenoid precursor, and a contraction of ring B in which $C_{(7)}$ appears as the carboxyl group of gibberellic acid. Once again, the groups at $C_{(4)}$ are isotopically distinct, implying that they are specifically derived from $C_{(2)}$ and the $C_{(3)}$-methyl group of MVA. The isotope distribution (CVI) suggests that the biogenesis of the phyllocladene-type ring follows a path similar to that proposed for the cyclization of rimuene to isophyllocladene (see above).

It is noteworthy that in the biosynthesis of the diterpenes the initiating cationoid entity is usually a proton, and in the triterpene series, an OH^+ or its equivalent. Exceptions are known to both modes—e.g. ambrein and the diterpenes hydroxylated in ring A. A number of the latter are now known and it is becoming clear that most, if not all of them, bear the oxygen function at $C_{(3)}$ where it is to be expected on biogenetic grounds (see hinokiol (LXX), cassaic acid (LXVII), darutigenol (XXXVII)).

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5

TROPYLIUM AND RELATED COMPOUNDS

T. Nozoe

The chemistry of tropolone and its related compounds, which started about fifteen years ago from studies on several kinds of natural products, has now been widely developed to form a complete new field in organic chemistry. The parent compound of this series of compounds, the tropylium ion (I), had already been obtained unknowingly in 1891 by Merling[1] by the thermal decomposition of 'dibromotropilidene'. It was after some sixty years that its true character was revealed by Doering and Knox[2]. This cation (I) is one of the triad of aromatic six π-electron systems—the three great families of aromatic compounds—which had been predicted by Hückel[3], the others being hexagonal benzene and pentagonal cyclopentadienyl anion (II).

I

II

Several reviews[4–10] have been published to date in this field and, because of the limit in space, this article will deal more specifically with the tropylium ion[11,12] and brief mention will be made of some of the important discoveries in this field during the past few years.

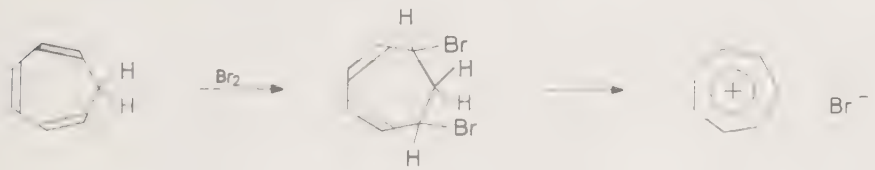
TROPYLIUM ION

Formation

Tropylium salts are now easily available substances, as is appropriate for the parent of aromatic compounds. The formation reactions for these substances may be classified into the following categories. The most important starting material for the synthesis of the ion (I) is tropilidene or cycloheptatriene (III), which is obtained in about 45 per cent yield by pyrolysis (at 450–500°) of bicyclo[2,2,1]hepta-2,5-diene (IV), formed by condensation of acetylene and cyclopentadiene[13].

IV III

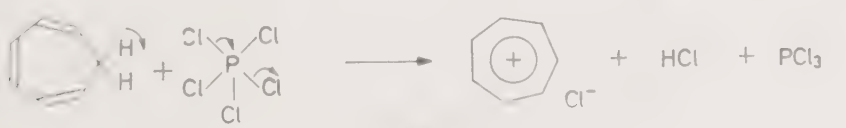
(*a*) *From tropilidene*—(*i*) *By bromination-dehydrobromination.* Heating dibromotropilidene (V) at 95–100°C (Merling–Doering process) gives tropylium bromide in 60 per cent yield[14]. The dibromide (V) liberates



V I

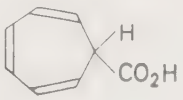
hydrogen bromide on being merely left to stand in liquid sulphur dioxide to give the tropylium bromide (I) in 70–80 per cent yield[15].

(*ii*) *By oxidation* (*dehydrogenation*). The cation (I) is very easily obtained from tropilidene (III) in the presence of a suitable acceptor for the hydride ion, or of an oxidizing agent. For example, addition of trityl perchlorate (or trityl bromide) to a solution of tropilidene in acetonitrile or sulphur dioxide quantitatively produces the cation (I) at a low temperature by hydride abstraction[16]. Vol'pin and others[17] found that the addition of two equivalents of phosphorus pentachloride to the solution of tropilidene in carbon tetrachloride resulted in almost quantitative formation of the cation (I). This process is very convenient for laboratory preparation of tropylium ion.



If the yield is of no account, numerous other processes are available for production of the cation (I). For example, the cation is obtained by the use of chromic acid, selenium dioxide, sulphuryl chloride, concentrated sulphuric acid and concentrated nitric acid[17]. Boron trifluoride and aluminium chloride cause side-reactions and the yield becomes very poor[17]. Chloranil and *p*-benzoquinone dibenzenesulphonimide alone fail to dehydrogenate tropilidene, but the presence of boron trifluoride in the latter case results in almost quantitative formation of tropylium salt[18]. The cation is also formed easily by electrolytic oxidation of tropilidene or ditropyl (XXXIII)[19].

(*b*) *From cycloheptatriene-carboxylic acid*—Oxidation of the carboxylic acid (VI) with potassium permanganate (acidic), periodic acid, potassium persulphate, lead tetra-acetate, or ceric ammonium nitrate gives[20] the cation (I). Application of the MERLING–DOERING method[14] to the acid (VI) gives carboxytropylium bromide[21] (VII), while acetylfluoroborate gives the cation in quantitative yield[22]. Tropylium fluoroborate is also obtained from the acid chloride of (VI), on treatment with excess of acetylfluoroborate[22].



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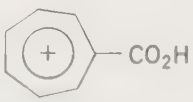

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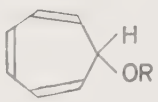
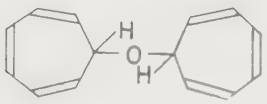
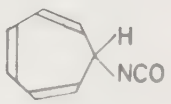


VIII

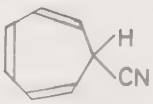
(*c*) *From tropyl compounds*—Pure tropylium salts are obtained in quantitative yield when dry ethereal solutions of alkyl tropyl ether (VIII) or ditropyl ether[2, 20] (IX) are saturated with dry hydrogen halide. Tropyl (norcaradiene) isocyanate (X) dissociates into tropylium isocyanate solution (more quickly by heating) in a polar



IX



X



XI

solvent[23]. On the contrary, cyanotropilidene (XI) does not form the tropylium salt unless in the presence of aluminium chloride or boron trifluoride[23]. The majority of tropilidene derivatives (XII and XIII) possessing a carbon side chain form tropylium salts by fragmentation reactions on treatment with a strong acid[24].

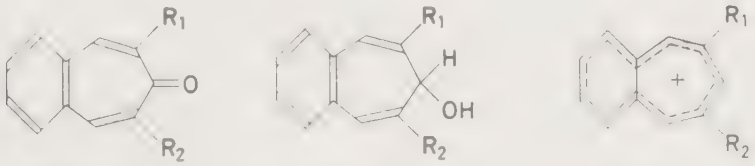
XII

XIII

(*d*) *Other processes*—(*i*) *From cyclo-octatetraene.* Oxidation of cyclo-octatetraene or its epoxide with potassium permanganate affords the cation (I); cycloheptatriene-carboxylic acid (VI) is assumed to be an intermediate in this reaction[25].

(*ii*) *From benzene.* Application of potassium t-butoxide to methylene halide in benzene gives tropylium halide, though in poor yield (1 per cent, as the chloride, 0·1 per cent, as the bromide). In this case, the initial reaction is thought to be addition of monohalocarbenes to benzene[26].

(*iii*) *From tropone.* The carbinol (XV) obtained by reduction of 3,4- or 4,5-benzotropone (XIV) with lithium aluminium hydride or sodium borohydride, forms a benzotropylium ion (XVI) on being dissolved in a strong acid[27]. This process is being utilized for the formation of polycyclic tropylium ions[28].



XIV XV XVI

(*iv*) *From alkylbenzene.* Formation of a tropylium ion by electron impact on toluene and other alkylbenzenes and on spiro-(2,4)-cyclohepta-(1,3)-diene in the gaseous state has been proved by mass spectroscopy[29,30] but the ion has not been isolated.

Physical Properties and Fine Structure

Tropylium salts in general have high melting points, do not dissolve in non-polar solvents but dissolve in hot acetonitrile and nitromethane, from which they can be recrystallized. When dissolved in alcohols or heated with them, the tropylium salt changes partly into tropyl alkyl ether. The bromide and, especially, the chloride are deliquescent and are freely soluble in water[2], but the perchlorate and the fluoroborate are sparingly soluble[23], while the tetraphenylborate[31] is entirely insoluble in water. The ion (I), having acidity comparable with acetic acid, is in equilibrium with tropyl alcohol in aqueous solution. This was indicated by observation of the ultraviolet spectra[2] of the ion (I) in solutions of different pH.

Soon after the isolation of tropylium bromide[2], many kinds of physico-chemical measurement were carried out, including infra-red and Raman spectra[32], ultraviolet absorption[16], polarography[33] and magnetic susceptibility[31], as well as molecular-orbital calculations[34–37]. All of these measurements and calculations are consistent with a structure for the tropylium ion having a planar heptagonal aromatic ring of D_{7h}-symmetry[32].

XVII

Vol'pin and others[38] treated the cation prepared from tropilidene labelled with ^{14}C, with phenylmagnesium bromide, and the 7-phenyltropilidene-^{14}C (XVII) so obtained was oxidized with potassium permanganate to benzoic acid. The specific activity of the benzoic acid obtained was just one-seventh (13·4 per cent) of that of the tropylium bromide used. This proves that the carbon–carbon bonds in the ring system of the ion (I) are completely equivalent, and that the positive charge is uniformly distributed among all the seven carbon atoms.

The foregoing facts lend strong support to the conclusion that the tropylium ion is the parent of the heptagonal aromatic ring system.

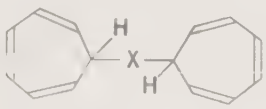
Chemical Properties

Tropylium ion is extremely stable as a carbonium ion, and even treatment for a long period with deuterium bromide–aluminium

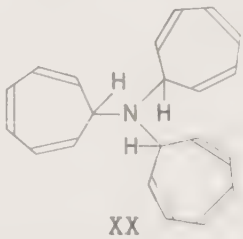
chloride at room temperature results in less than 1 per cent of deuterium-hydrogen exchange[39]. Due to the full positive charge, however, the ion undergoes easy reaction with various bases (anionoid reagents)[11,12], and the reaction may be classified into the following three kinds:

(*a*) *Tropylation*—(*i*) This is one of the typical reactions between the tropylium ion and an anionoid reagent[11], and the yield is generally good, giving products formulated as (XVIII) to (XX).

XVIII



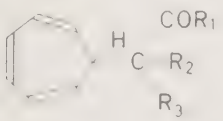
XIX



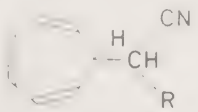
XX

Reaction with alkoxides, mercaptides, alkylamines and acid amides gives monotropyl compounds (XVIII; X = OMe, OEt, $OCH_2C_6H_5$, SMe, NHEt, $NHCOCH_3$ and succinimide, etc.); reaction with alkali, aqueous ammonia and hydrogen sulphide gives ditropyl compounds (XIX; X = O, S, NH), and tritropylamine (XX) is formed by the reaction with ethereal ammonia[11,14,24,40]. Tropyl derivatives (XVIII; X = CN, alkyl, aryl, cyclopentadienyl) are obtained on reaction with alkali cyanide, Grignard reagents, phenyllithium and sodium cyclopentadienide[14,41].

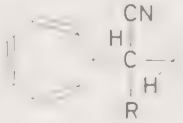
(*ii*) The cation (I) undergoes reaction with various compounds which are capable of forming carbanins, such as carboxylic acids or esters, aldehydes, ketones, and nitroalkanes, to form products of the type (XXI). It also forms tropyl derivatives (XXII or XXIII; R = CN, CO_2Et or alkyl group) by reaction with malononitrile, ethyl cyanoacetate and alkyl cyanide[24,40,41].



XXI



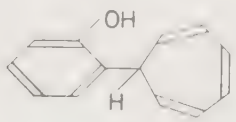
XXII



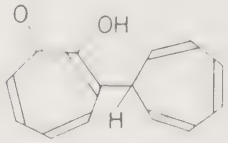
XXIII

(*iii*) The tropylium ion reacts with alkali phenoxide or tropolonate to form *o*-tropylphenol (XXIV) or 3-tropyltropolone (XXV)[41,45b]. The fact that the position *ortho* to the phenol is attacked is

ascribed to the initial formation of the *O*-tropyl ether which soon undergoes Claisen rearrangement in the cold.



XXIV

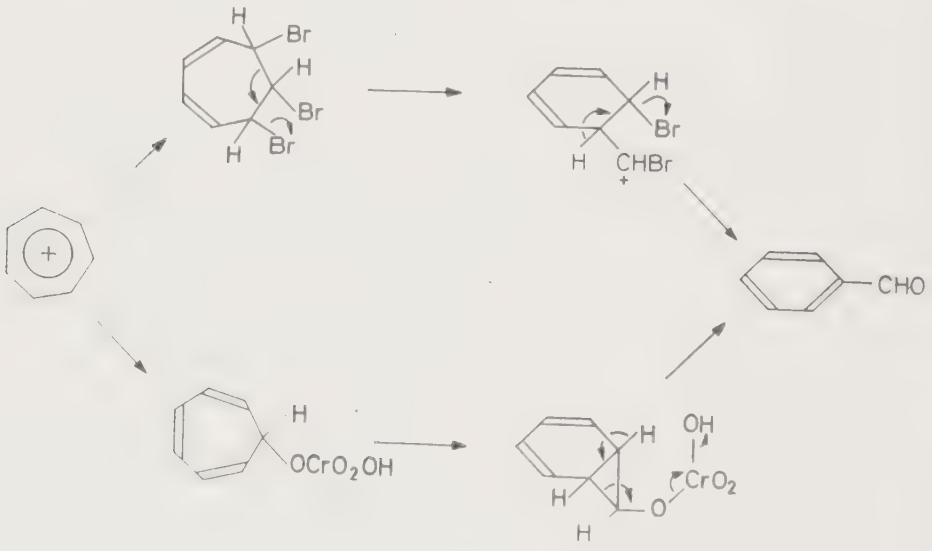


XXV

(*iv*) The tropylium ion undergoes addition with compounds possessing active double bond (vinyl ethers, etc.) or triple bond (phenylacetylene)[41]. The tropylation reaction is not limited to the cation (I) but occurs also with alkyl ethers or ditropyl ether[40, 41].

(*b*) *Rearrangement*—The tropylium ion gives tropone on oxidation with pyridine chromic acid complex[42] but forms benzaldehyde with the majority of oxidizing agents. For example, potassium permanganate in neutral medium[23], chromic acid in acetic acid[14] and silver oxide in aqueous solution, or addition of bromine to tropylium bromide in ethanol and subsequent dissolution of the product ($C_7H_7Br_3$) in water[23], all give a good yield of benzaldehyde. It is assumed that this rearrangement takes place through an intermediate of norcaradiene-type or the corresponding tropilidene-type[14, 23].

Oxidation of tropylium bromide in aqueous solution with hydrogen peroxide gives benzene and formic acid (or carbon monoxide) in a



good yield, with a small quantity of phenol. In this case, a peroxide (XXVI) is considered to be formed as an intermediate, as shown[26]:

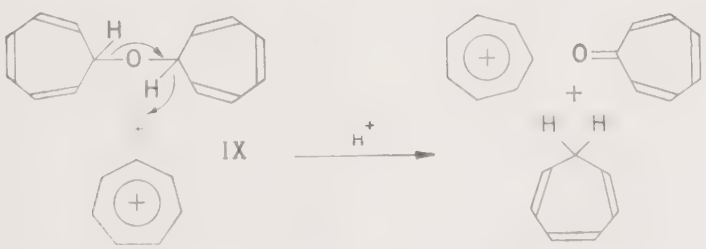
XXVI

(*c*) *Oxidizing properties*—(*i*) *Disproportionation.* Tropylium ion is able to abstract a hydride ion from easily oxidizable substances, and is thereby converted into tropilidene, though the action is not strong. For example, slow neutralization of an aqueous solution of a tropylium salt with sodium bicarbonate results in the formation of tropone (XXVIII) by dehydrogenation of tropyl alcohol (XXVII) initially formed from the cation (I)[43, 44].

In the writer's laboratory[43] it was found that when a minute quantity of concentrated hydrochloric acid or tropylium ion was added to

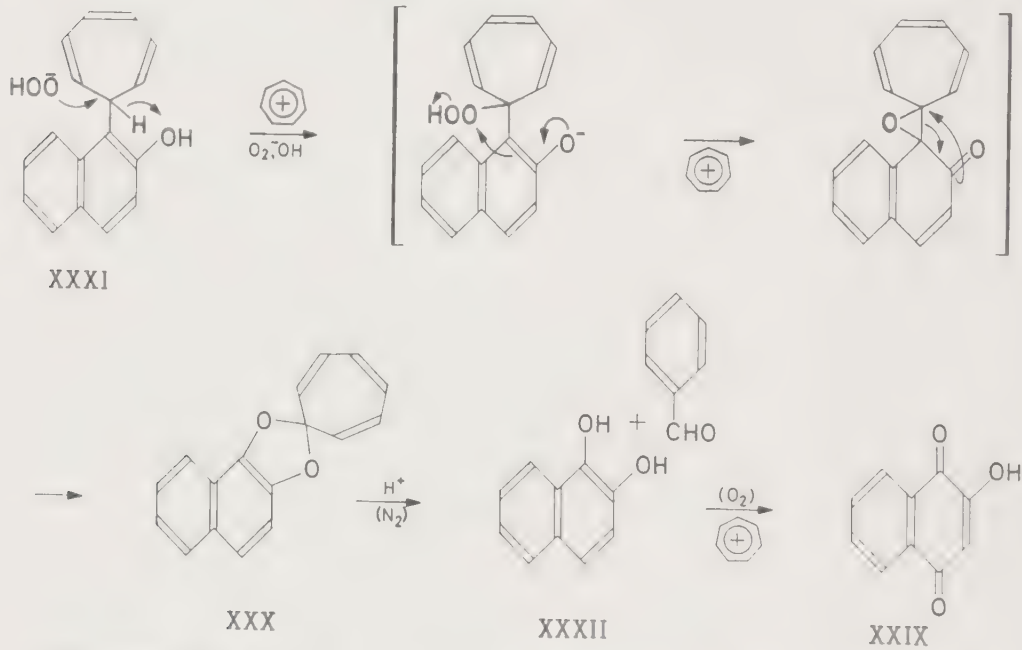
XXVII XXVIII

ditropyl ether (IX), and the resulting liquid was distilled after standing for some time, tropilidene and tropone were obtained in equimolar quantities. Independently of this work, Dreiding in Switzerland and chemists in the Shell Laboratories[44] in the Netherlands found that the same products were obtained when silica gel treated with acid was



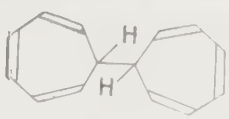
added to ditropyl ether before distillation[44]. This reaction is now utilized as one of the most convenient processes for the preparation of tropone and tropolone[43].

(*ii*) *Oxidation of phenols.* Vol'pin and others reported that tropylium ion reacts with phenol, α- and β-naphthols and hydroquinone on heating, and with resorcinol and phloroglucinol in the cold to form tropylated derivatives[40], but details of the reaction are not available as yet. Nozoe and others[45a] found that reaction of the cation and sodium β-naphtholate gave 2-hydroxy-α-naphthoquinone (XXIX) besides a neutral substance. Further detailed investigations revealed the route of this reaction[45b]. It was found that 1-tropyl-2-naphthol (XXXI), first formed, undergoes autoxidation in dilute alkaline solution to form a ketal (XXX), identical with the neutral substance obtained before. Decomposition of the ketal (XXX) with acids in air results in the formation of benzaldehyde and a hydroxyquinone (XXIX). Treatment of the ketal (XXX) with acid in a nitrogen atmosphere, however, results in the formation of benzaldehyde and 1,2-dihydroxynaphthalene[45b] (XXXII).

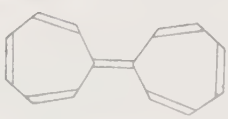


XXXI XXX XXXII XXIX

(*iii*) *Reduction product.* Catalytic reduction of tropylium salts in glacial acetic acid gives cycloheptane, while reduction with zinc dust gives bitropyl (XXXIII). Bromination-dehydrobromination of (XXXIII) yields heptafulvalene[12, 46] (XXXIV).



XXXIII



XXXIV

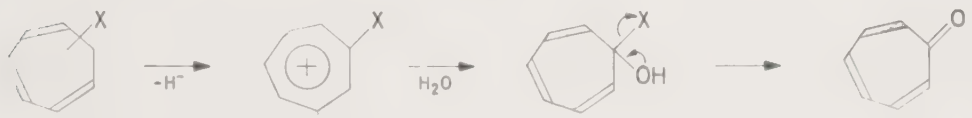
SYNTHESES OF TROPONES AND TROPOLONES

New Methods of Synthesis

(*a*) *From tropilidene or tropylium ion*.—Oxidation of tropilidene (III) or tropylium ion (I) with chromic acid-pyridine[42] or direct oxidation of (III) with selenium dioxide[47] gives tropone (XXVIII) in 30–40 per cent yield. The latter process, due to SUNAGAWA[47], and the disproportionation method (see above) using ditropyl ether (80 per cent of the theoretical yield)[43, 44], provide convenient routes for the preparation of tropone.

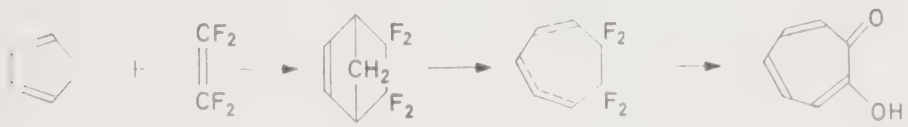
Conversion of tropone into tropolone through 2-aminotropone has already been effected[48], and tropolone is now a fairly easily accessible substance. This process has been utilized for the preparation of 4- or 5-phenyltropolone from 7-phenyltropilidene[43] and also in a synthesis of colchicine[49].

(*b*) *From halogenated cycloheptatriene or cycloheptadiene*—Tropone is produced when halogeno- or methoxytropylium ion (XXXVI; X = Br or OMe) obtained from substituted tropilidene (XXXV; X = Br or OMe) is poured into water[16, 50] or when tetrabromotropilidene is heated for a long time (30–40 per cent)[15, 43].



XXXV XXXVI

DRYSDALE and others[51] found that tetrafluorocycloheptadienes (XXXVIII), obtained by pyrolysis (at 700–750°) of a condensation product (XXXVII) of cyclopentadiene and tetrafluoroethylene, underwent hydrolysis when heated with potassium acetate in aqueous acetic acid at 120–130° to form tropolone in an overall yield of 20 per cent.



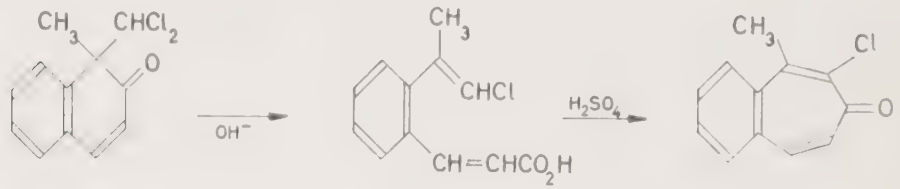
XXXVII XXXVIII

(*c*) *By enlargement of a six-membered ring*—(*i*) *From halomethyl compounds*. 4-Dichloromethyl-4-methyl-2,5-cyclohexadienone oxime

(XXXIX) forms 4-methyltropone oxime (XL) in 22 per cent yield by the action of alkali[52]. This ring-enlargement reaction has recently been utilized in a total synthesis of colchicine[53].

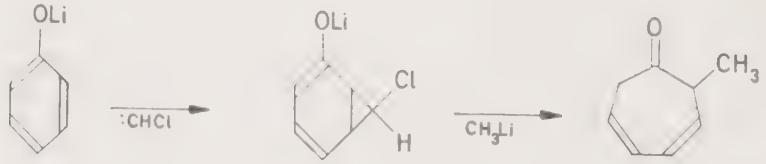
XXXIX XL

Similarly, the 4,5-benzotropone derivative (XLII) is obtained from the 2,2-disubstituted ketone[54a] (XLI).



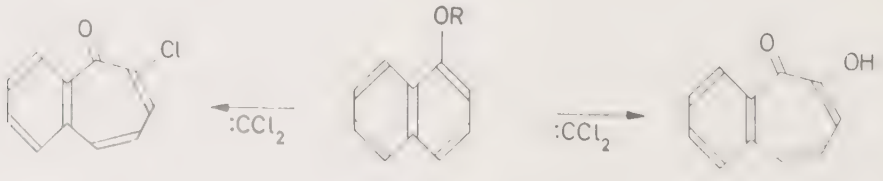
XLI XLII

(*ii*) *From phenols.* When methyllithium is added to a solution of lithium phenoxide (XLIII) in methylene chloride, 2-methylcyclohepta-3,5-dieneone (XLIV) is obtained (33 per cent); addition of an equimolar amount of bromine to this product results in easy dehydrogenation to 2-methyltropone[55].



XLIII XLIV

7-Chloro-2,3-benzotropone (XLVI) and 3,4-benzotropolone (XLVII) are obtained by addition of dichlorocarbene to α-naphthyl alkyl ether[54b] (XLV).

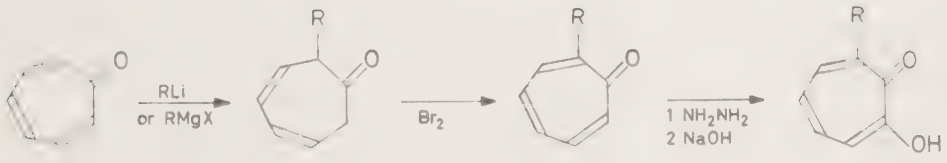


XLVI XLV XLVII

(*d*) *Direct synthesis of tropone ring*—One-step synthesis of the tropone nucleus is so far limited to the syntheses of 4,5-benzotropones and 4,5-benzotropolones[8–10]. A tropone complex (XLVIII) has, however, recently been obtained, in small quantity, by the addition of acetylene to iron carbonyls, $Fe_2(CO)_9$ and $Fe_3(CO)_{12}$, in non-polar solvent[56].

XLVIII

(*e*) *Alkylation or arylation of troponoids*—(*i*) *From tropone.* As in the case of tropolone or its methyl ether[8–10], addition of organometallic compounds to tropone, now easily available, leads to dihydrotropones (XLIX), which are conveniently dehydrogenated to give 2-substituted tropones[55,57] (L).



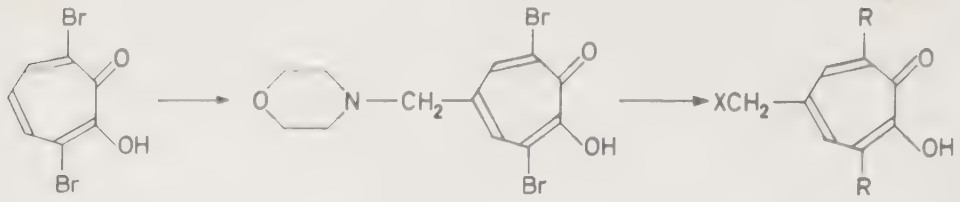
XLIX L LI

(*ii*) *Hydroxymethylation and aminomethylation.* Hydroxymethylation and aminomethylation of tropolones tend to occur preferentially at the 3- or 7-positions[8–10]. Oxidation of 3-hydroxymethyltropolones (LII; R = H or iso-C_3H_7) with active manganese dioxide produces 3-formyltropolones (LIII) which can be converted into various condensation products[58].

LII LIII

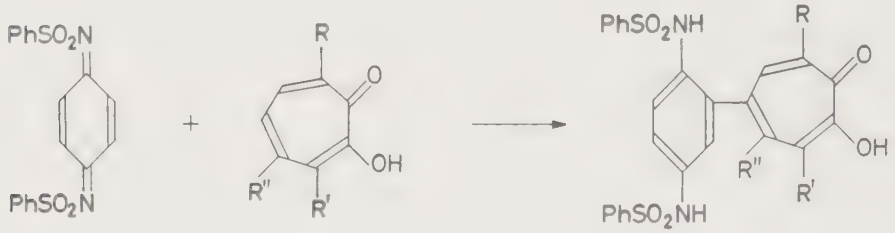
Seto and others[59] carried out the Mannich reaction of 3,7-dibromotropolone (LIV) to form 3,7-dibromo-5-morpholinomethyltropolone (LV) and prepared from it various derivatives (LVI; R = H

or Br, X = H, alkyl, OH, mercapto, amino-acid residue, etc.) possessing a variety of side chains in the 5-position.



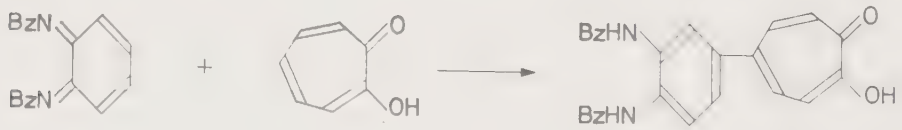
LIV LV LVI

(*iii*) *Condensation with quinone derivatives.* SETO and his collaborators[60] found that application of *p*-benzoquinone dibenzenesulphonimide to tropolone, in the presence of triethylamine, resulted in easy condensation, forming 5-aryltropolone derivatives of the type (LVII; R,



LVII

R′, R″ = H, Br or iso-C_3H_7). This reaction has been applied to *p*-benzoquinone and its monobenzene-sulphonimide, and to *o*-benzoquinone dibenzimide[60]. In the latter case, the product is a compound formulated as (LVIII).



LVIII

Synthesis of Some Natural Tropolones

The natural tropolones known to date total less than forty in number, including those of terpenoid origin, microbial metabolites and colchicum alkaloids[10]. Of these, the structures of fifteen compounds have been determined; the three thujaplicins, *β*-thujaplicinol, stipitatic acid and puberulic acid were synthesized at a comparatively early stage[9, 10]. A few more have been synthesized during the past

few years, and total syntheses of the most complicated and interesting natural tropolone, colchicine, have very recently been completed.

(*a*) *β-Dolabrin and its isomers*—*β*-Dolabrin (LIX) was first isolated[61] from the essential oil of *Thujopsis dolabrata* Sieb. et Zucc. and was later found in the heart-wood of several conifers[62], but its isomers have not been found in nature, in contrast to the thujaplicins.

In general, application of Grignard reagents to free tropolones results in precipitation of a sparingly soluble complex, and introduction of other functional groups into the tropolone ring by further application of the reagent becomes extremely difficult. In the writer's laboratory[63] the octyl ester (LX) of 5-carboxytropolone was prepared in order to make the initially formed complex soluble in organic solvents; reaction of excess methylmagnesium bromide with this ester was found to give a

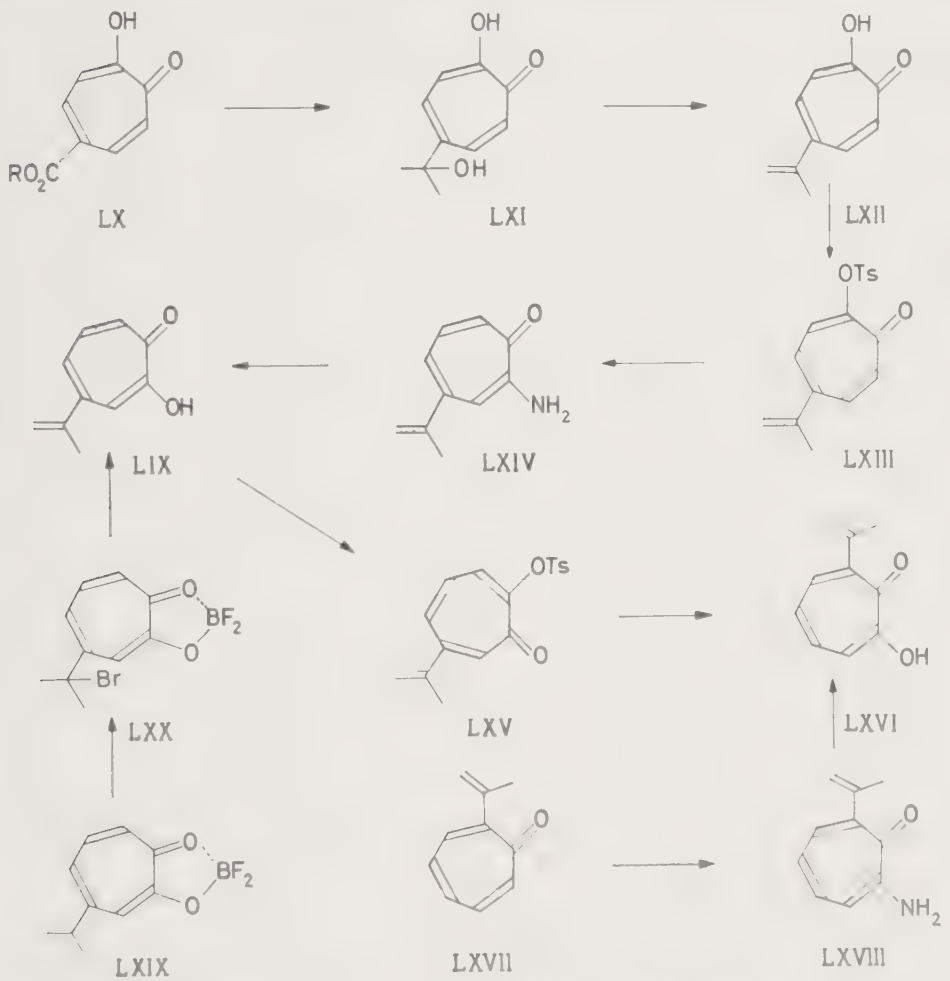


Figure 1. Syntheses and Mutual Transformation of Dolabrins

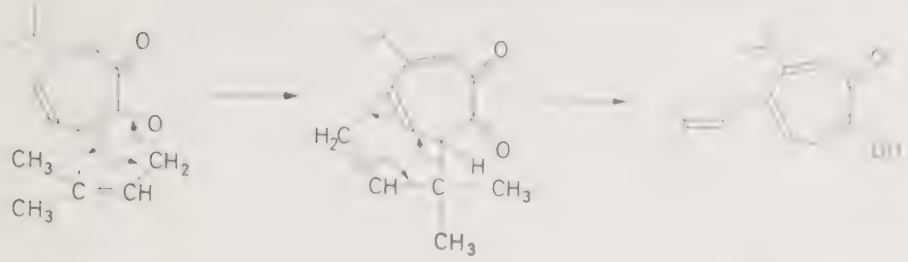
small quantity of 5-acetyltropolone and a tertiary alcohol (LXI). Dehydration of (LXI) gave γ-dolabrin (LXII). Treatment of γ-dolabrin tosylate (LXIII) with ammonia gave, besides the rearrangement product, an abnormal substitution product, the aminotropone (LXIV), whose alkaline hydrolysis finally produced β-dolabrin (LIX), identical with the natural product. β-Dolabrin forms two tosylates, one of which was converted to the γ-isomer by the process, while amination followed by hydrolysis of the isomeric tosylate (LXV) produced α-dolabrin (LXVI), though in poor yield. Amination, with abnormal substitution, of 2-halo or especially 2-tosyloxytropones is a convenient process, in general, for preparation of isomers of various tropolones[64].

β-Dolabrin was also synthesized by SETO and MATSUMURA[65b] *via* the boron difluoride complex of 8-bromohinokitiol (LXX), itself obtained from the hinokitiol complex (LXIX) by bromination. Side-chain bromination in a troponoid was observed first by KIKUCHI[65a] in the case of 2-bromo-7-methyltropone, giving the compound (LXXI).

LXXI

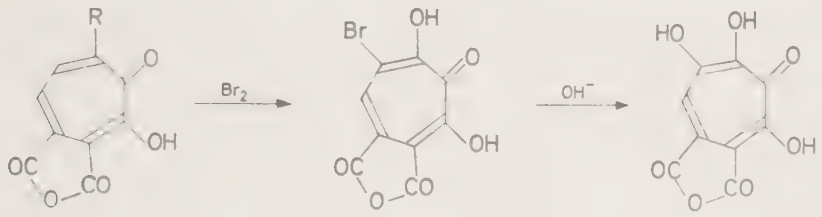
(*b*) *Nootkatin*—Nootkatin (LXXIII) is the only sesquiterpenoid tropolone known and was first isolated[66] from *Chamaecyparis nootkatensis* Spach., but was later found to be distributed fairly widely in various conifers[62]. Although its structure was established rather early[66], its synthesis was not effected until quite recently. In the writer's laboratory, an attempt was made to utilize the Mannich reaction[59] with 3,7-dibromo-4-isopropyltropolone, but the morpholinomethyl group entered the 7-position, liberating its bromine, and the objective was not attained[67].

Although the Claisen rearrangement of tropolones is known to take place into the 3- or 7-positions[68], KITAHARA and others[68b] found that 5-substituted tropolone could also be obtained from the γ,γ-dimethylallyl ether (*para* rearrangement). Using this reaction, β-thujaplicin γ,γ-dimethylallyl ether (LXXII) was heated in xylene, and a compound identical with natural nootkatin was obtained in *ca.* 7 per cent yield[68b].



LXXII LXXIII

(*c*) *Puberulonic acid and its isomers*—Puberulonic acid (LXXVI) was synthesized[69] by alkaline hydrolysis, in the presence of sodium β-naphthalene sulphonate, of 7-bromotropolone-3,4-dicarboxylic anhydride (LXXIV; R = Br) to the 7-hydroxy compound (LXXIV; R = OH), followed by bromination and hydrolysis as indicated in the scheme.



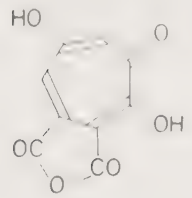
LXXIV LXXV LXXVI

Stipitatonic acid was first obtained from the culture media of *Penicillium stipitatum* Thom. Since this compound easily underwent decarboxylation to form stipitatic acid and formed a reddish brown compound by azo coupling, formula (LXXVII) rather than (LXXVIII) was first adopted for this acid[70a].

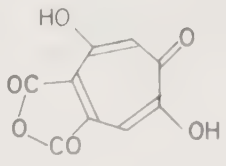
Kitahara and others[71] obtained the 6-hydroxy compound (LXXVII) besides the 7-hydroxy compound (LXXIV; R = OH)[69] by treatment of the 7-bromo compound (LXXIV; R = Br) with alkali[9,10]. The third isomer (LXXIX) was obtained by persulphate oxidation of the dicarboxylic acid, but all these isomers were found to be different from natural stipitatonic acid, and it was assumed by these authors that the structure of stipitatonic acid must be (LXXVIII)[71].

Independently of this work, Segal[70b] re-examined previous studies and adopted the formula (LXXVIII) for the same acid, withdrawing the formerly proposed formula (LXXVII), since alkali fusion of stipitatonic acid afforded 6-hydroxybenzene-1,2,4-tricarboxylic

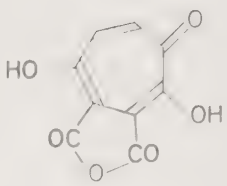
acid[70b]. As far as the present writer is aware, synthesis of stipitatonic acid has not been reported to date.



LXXVII

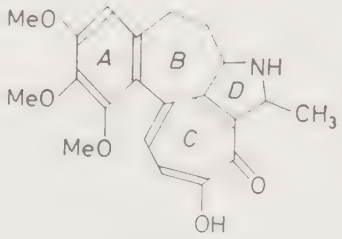


LXXVIII



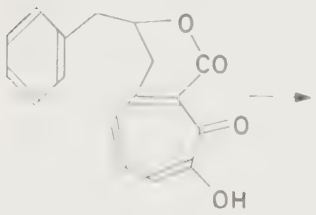
LXXIX

(*d*) *Colchicine*—Since the early period of the development of tropolone chemistry, efforts have been made by chemists all over the world to achieve a total synthesis of colchicine. Until very recently these were unsuccessful. Some time ago, WOODWARD and his school synthesized the tetracyclic tropolone (LXXX) through some twenty steps of interesting procedures, starting with *β*-(3,4,5-trimethoxyphenyl) propionic acid. However, attempted cleavage of the D-ring (pyrroline ring) by the Hofmann degradation resulted in cleavage in an unexpected direction, and this process failed to give the desired compound[72].

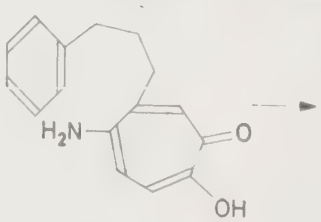


LXXX

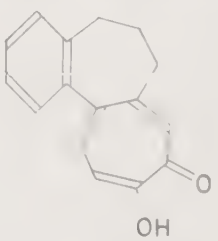
As a preliminary experiment for colchicine synthesis, the aminotropolone (LXXXII) was prepared from the condensation product (LXXXI) of phenylacetaldehyde and 3-carboxy-4-carboxymethyltropolone. Pschorr reaction of (LXXXII) finally gave the tricyclic



LXXXI



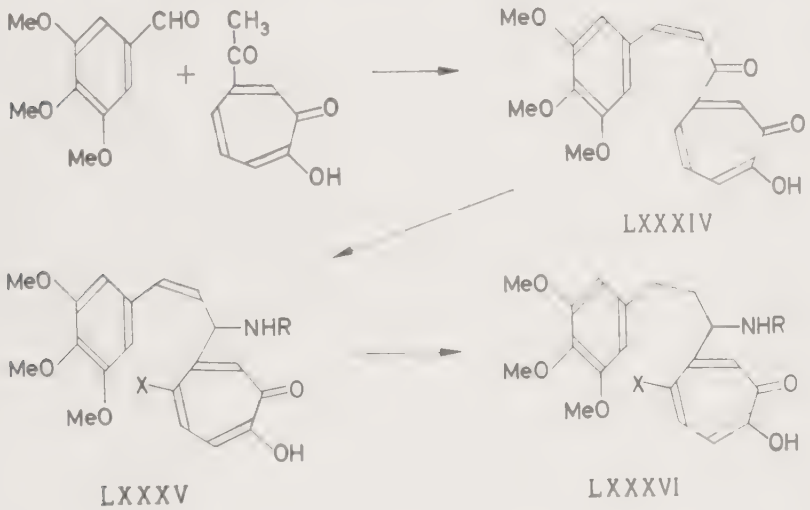
LXXXII



LXXXIII

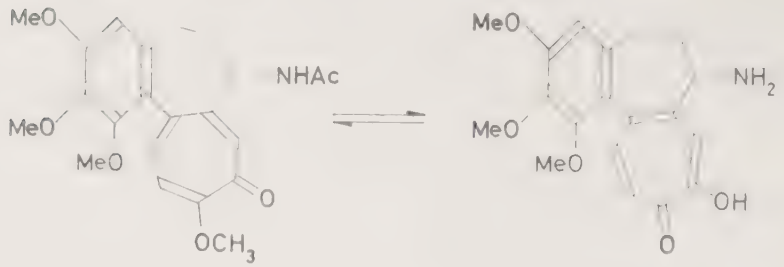
tropolone (LXXXIII), the parent compound of colchicine, although the yield was rather poor (5 per cent)[73a]. The same condensation was attempted with 3,4,5-trimethoxyacetaldehyde, but no reaction took place.

Condensation of 3,4,5-trimethoxybenzaldehyde and 4-acetyltropolone gave 4-(3′,4′,5′-trimethoxycinnamoyl)tropolone (LXXXIV), whose oxime was reduced to the amino compound (LXXXV; R = X = H), and the Pschorr reaction carried out on the 5-amino derivative (LXXXV; R = Ac, X = NH_2). The required compound was not obtained, however; the deamination product (LXXXV; R = Ac, X = H) besides unidentified compounds was formed. The double bond in (LXXXV) resists reduction, but hydrogenation over a large quantity of palladium–charcoal gave the bicyclic tropolone (LXXXVI; R = Ac, X = H), an open-chain analogue of colchicine[73b]. The Pschorr reaction of its amino derivative (LXXXVI; R = Ac, X = NH_2) is still under investigation, but its ring closure seems to be difficult.



At this stage of the investigation total synthesis of colchicine was reported from two other laboratories (see below).

Partial synthesis from desacetylcolchiceine—As a preliminary step to total synthesis of colchicine (LXXXVII), Corrodi and Hardegger[74] carried out experiments on the racemization of the *N*-benzylidene derivative of desacetylcolchiceine (trimethylcolchicinic acid) (LXXXVIII) and resynthesis of optically active colchicine[74] from the racemic (LXXXVIII).



LXXXVII LXXXVIII

Total synthesis by Eschenmoser—ESCHENMOSER and others[53] started with dimethoxyhydroxybenzosuberone[75] (LXXXIX) derived from purpurogallin trimethyl ether, and converted it in a series of sixteen reactions into desacetylcolchiceinamide (XCIII; $R = X = NH_2$). The route of this synthesis is given in *Figure 2*. In this case, conversion

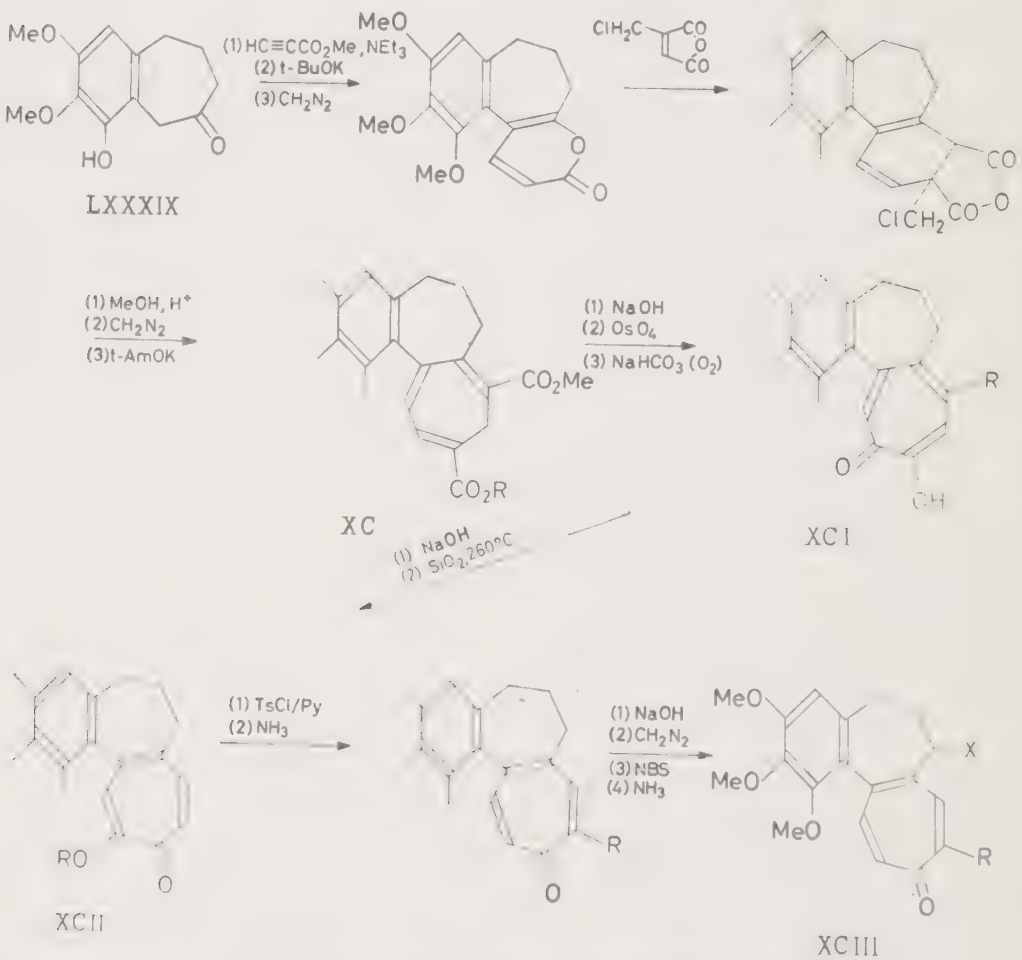


Figure 2. Colchicine Synthesis by Eschenmoser

of the cycloheptatrienedicarboxylic acid (XC) to the tropolone derivative (XCI) was effected by air oxidation of the osmium tetroxide-complex in weakly alkaline medium (20–30 per cent yield). Conversion of the tropolone (XCII; R = H) to its isomer (XCIII; R = OH) utilized the abnormal ammonolysis of the tosylate (XCII; R = Ts) described earlier[63, 64, 76].

Total synthesis by van Tamelen—The process used by VAN TAMELEN and his associates[77] started with trimethoxybenzosuberone[75] (XCIV), obtained from purpurogallin tetramethyl ether, and reached desacetylcolchiceine (XCVIII; R = H, X = NH_2) in fourteen steps. The route of this synthesis is summarized in *Figure 3*.

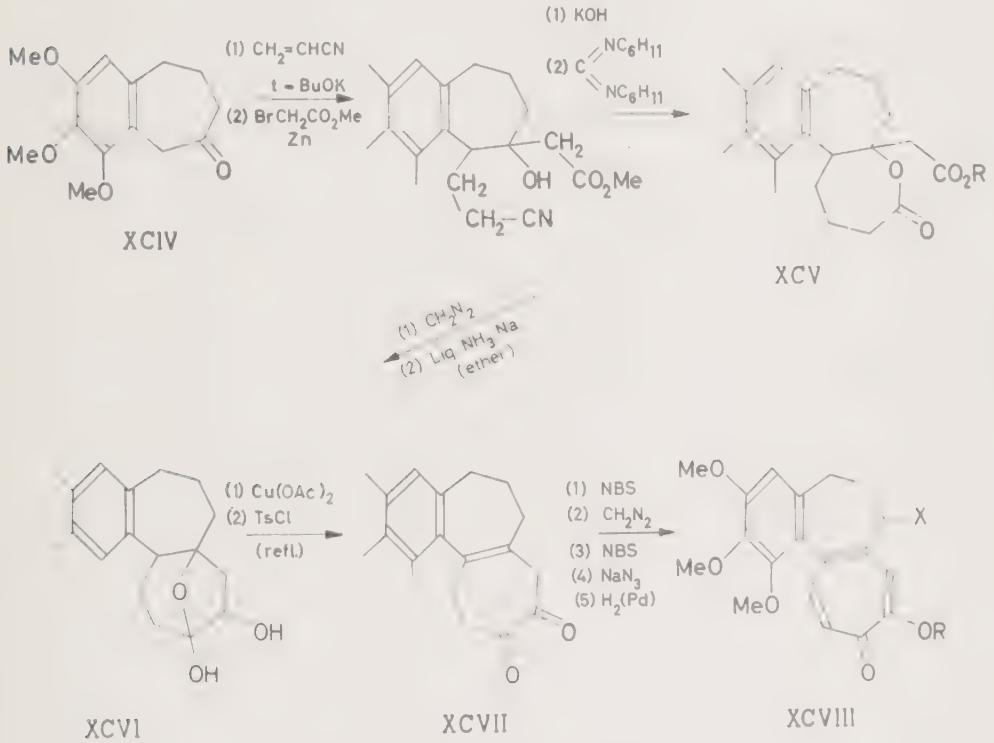
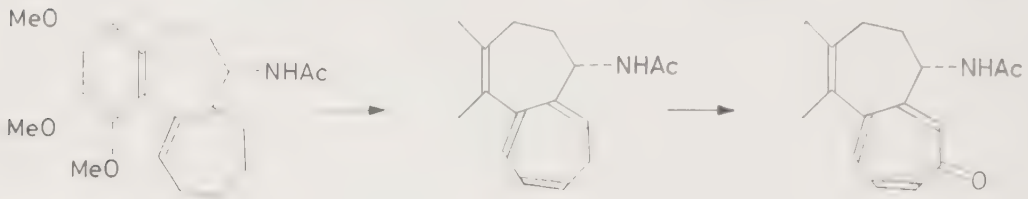


Figure 3. Total Synthesis by van Tamelen

In this synthesis, the intramolecular acyloin condensation of the lactone ester (XCV) was carried out at −37·4°C with sodium and liquid ammonia in anhydrous ether to give the hydroxyhemiketal (XCVI). cycloHeptenedione (XCVII) was dehydrogenated with *N*-bromosuccinimide to form the tropolone derivative (XCVIII; R = X = H).

From hexahydrodemethoxydesoxycolchicine—Some time ago, RAPOPORT and others[78] prepared from colchicine (LXXXVII), hexahydrodemethoxydesoxycolchicine (IC), which retains the original ring system of colchicine. Very recently, colchicine has been synthesized by NAKAMURA[49, 79] starting with this compound (IC). The cycloheptatriene derivative (C) obtained from it was converted to colchicide (CI) and its isomer through the tricyclic tropylium ion and related ditropyl



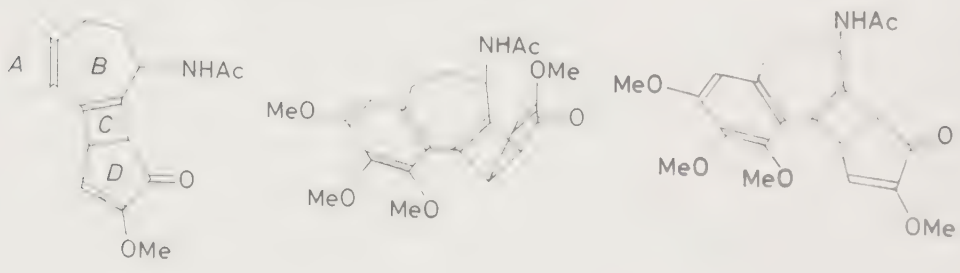
IC C CI

ether (Nozoe–Dreiding method). This compound (CI), present in a crude mixture, was aminated with hydrazine to form colchiceine amide, thereby establishing a third possible synthetic procedure.

SOME REACTIONS OF TROPONOID COMPOUNDS

Photochemical Transformation

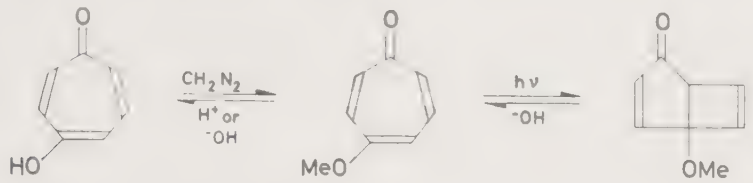
Of the three isomeric lumicolchicines obtained by ultraviolet irradiation of colchicine, two (β and γ) have been found as minor constituents among colchicum alkaloids[9, 10, 80]. FORBES[81] concluded from the results of degradation studies on the β- and γ-isomers that this photochemical transformation was due to formation of a tetracyclic compound (CII) by valence tautomeric change of the tropolone ring (C-ring) in colchicine. He assumed that the asymmetric centre of colchicine was unaffected by the reaction, and that β- and γ-lumicolchicines existed as diastereoisomers. Further, GARDNER and



CII CIIa CIIb

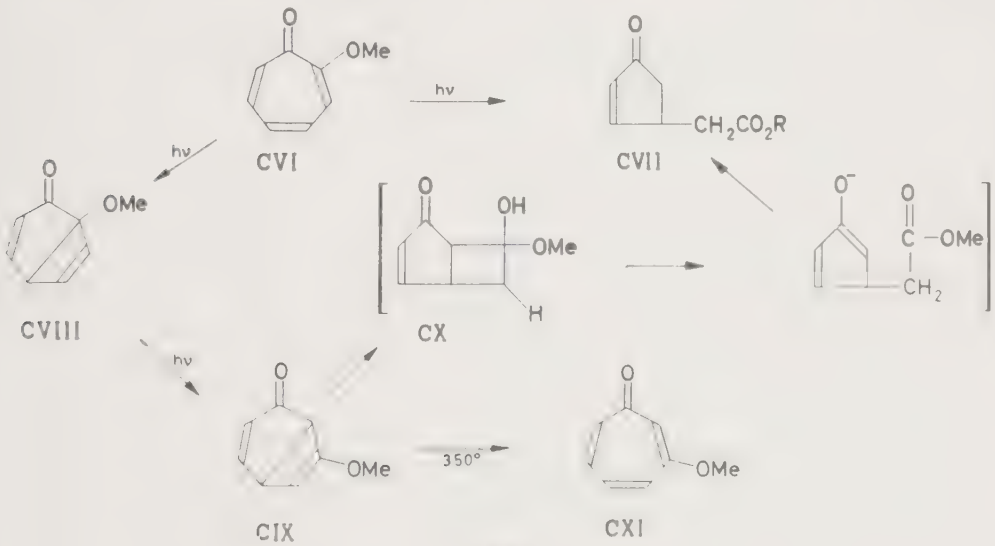
others[82] inferred the configurations of (CIIa) and (CIIb), respectively, for the β- and γ-isomers from the extinction coefficients of the ultraviolet spectra and the behaviour of the two isomers on catalytic reduction.

Studies on photoisomerization of simpler monocyclic tropolones have recently been carried out. CHAPMAN and others[83] found that irradiation of an aqueous solution of 4-methoxytropone (CIII) produced an unsaturated, bicyclic ketone (CIV) which underwent slow hydrolysis with dilute acid to form 4-hydroxytropone (CV), while it reverted, very rapidly and in quantitative yield, to the original compound (CIII) by the action of dilute sodium hydroxide at room temperature.



CV CIII CIV

Ultraviolet irradiation of tropolone or tropolone methyl ether (CVI) was found to give 3-oxocyclopentenylacetic acid or its methyl ester (CVII; R = H or CH_3)[84,85]. DAUBEN and others[84b] made a detailed examination of this reaction and found that irradiation of the methyl ether (CVI), under some special conditions, first produced the unstable valence tautomer (CVIII) which, on further irradiation, produced the second tautomer (CIX). Treatment of this tautomer

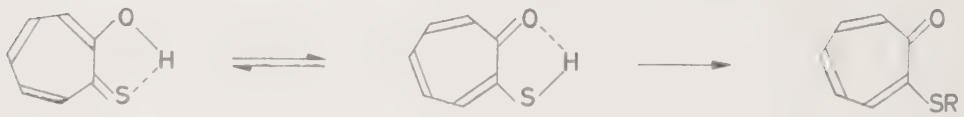


with aqueous acid resulted in ring opening to form the compound (CVII; R = Me). The hemiketal (CX) was assumed to be an intermediate in the change from (CVIII) to (CVII)[84b]. Heating of the second intermediate (CIX) at 350° results in formation of 3-methoxytropone (CXI), showing the former to be a valence tautomer of the latter[84b]. Reaction mechanisms for these interesting photochemical reactions were suggested[83–85].

Troponethiones and Troponeimines

The structure of reddish-orange 2-mercaptotropone[86] (CXII), obtained by the action of sodium hydrogen sulphide on 2-halotropone and of its isopropyl homologues[87], has been re-investigated.

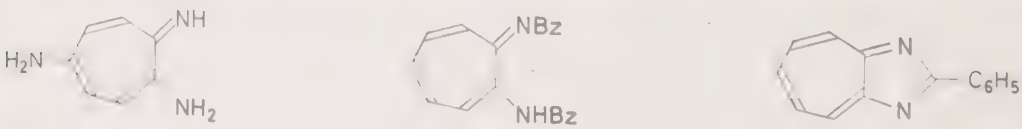
2-Mercaptotropone is considered to be an equilibrium mixture of (CXIIa) and (CXIIb)[86]. Although the chemical reactions to give S-substituted derivatives (CXIII) implied the predominance of the



CXIIa CXIIb CXIII

structure (CXIIb), physical measurements such as ultraviolet and infra-red spectra, nuclear magnetic resonance spectrum and dissociation constant, revealed the predominance of the structure (CXIIa) in the ground state[88].

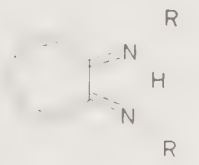
Some time ago, 2,5-diaminotroponeimine (CXIV) was prepared in the writer's laboratory by reduction of tropoquinone trioxime, and was converted into 1,3-diaza- or 1,2,3-triaza-azulene[89]. The Schotten-Baumann benzoylation of 1,3-diaza-azulene gave 2-aminotroponeimine



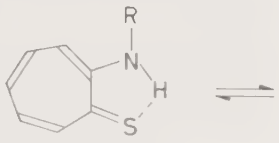
CXIV CXV CXVI

dibenzoate (CXV), alkaline hydrolysis of which brought about recyclization to 2-phenyl-1,3-diaza-azulene (CXVI); the free 2-aminotroponeimine was not obtained[90].

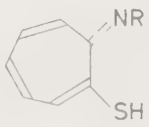
More recently, however, free 2-aminotroponeimine and its derivatives (CXVII) were obtained in the laboratory of Du Pont[91] by reaction of tetrafluorocycloheptadienes (XXXVIII) with ammonia or primary amines. Action of hydrogen sulphide on the compound (CXVII; R = H, Me, *p*-tolyl) resulted in substitution of the imino group by sulphur to form the compound (CXVIII). Through examination of its absorption spectra and nuclear magnetic resonance spectrum, it was found that the two nitrogen atoms in the compound (CXVII) are equivalent and that the compound (CXVIII) possessed a 2-amino-troponethione structure (CXVIIIa) rather than (CXVIIIb).



CXVII



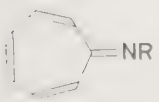
CXVIIIa



CXVIIIb

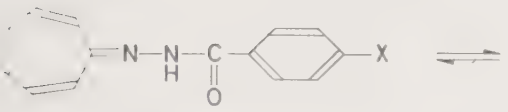
Both (CXVII) and (CXVIII) form stable chelate complexes with Cu^{++}, Ni^{++} and Co^{++}, and the amino-imine (CXVII) undergoes bromination and azo-coupling in its 5-position, showing a fair degree of aromatic character.

Troponeimine (CXIX; R = H) itself is not known as yet but tropone oxime (CXIX; R = OH) and many of the semicarbazones and arylhydrazones, all highly coloured substances, have been obtained[92].

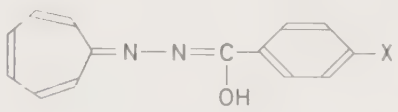


CXIX

It is interesting to note that some of the benzoylhydrazones of tropone are obtained in two forms, keto (CXXa) and enol (CXXb) forms; similar behaviour is shown by



CXX a



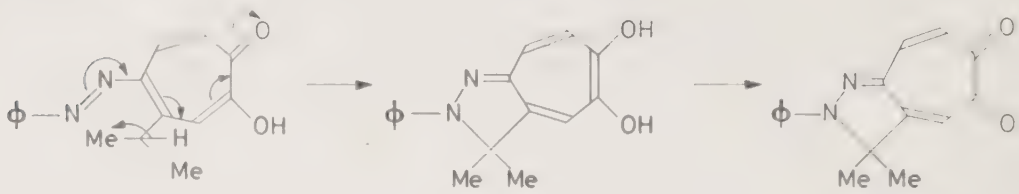
CXX b

the picrates[93]. The equilibria are greatly affected by the polar effect of the substituent (X) in the benzene ring.

Cyclization of Arylazotropolones and Related Compounds

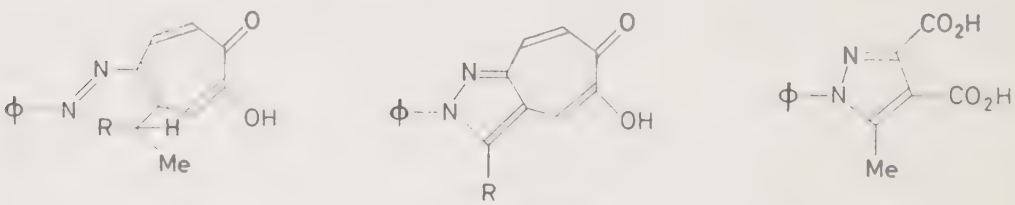
Heating of 5-arylazohinokitiol (CXXI) above its melting point or heating in the presence of benzoquinone results in concurrent cyclization and dehydrogenation to give hinopurpurin (CXXII) in a good

yield[94]. It had been believed that such changes do not take place in 4-methyl- and 4-ethyltropolones.



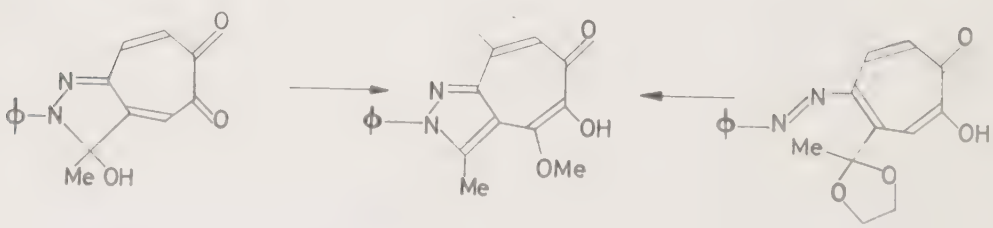
CXXI CXXII

More recent studies, however, have shown that arylazo compounds of 4-ethyl-, 4-(α-hydroxyethyl)- and 4-(α-acetylaminoethyl)tropolones (CXXIII; R = H, OH, or NHAc), undergo cyclization when heated in ethanol to form a pale yellow, acidic substance (CXXIV;



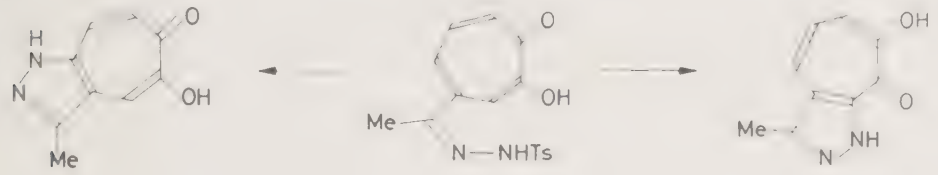
CXXIII CXXIV CXXV

R = Me). Since this substance gives the pyrazole-dicarboxylic acid (CXXV) by oxidation with potassium permanganate, the product must have the structure[95] (CXXIV). 5-Arylazo-4-methyltropolone does not undergo cyclization under the same conditions but does so when heated with addition of iodine, to form a pyrazolotropolone (CXXIV; R = H). Azo coupling of 4-acetyltropolone gives rise to the purple heterocyclic compound (CXXVI), reduction of which gives the compound (CXXIV; R = Me), whereas the action of acid in methanol gives the compound (CXXVII) which is also formed from the ethylene ketal[95] (CXXVIII).



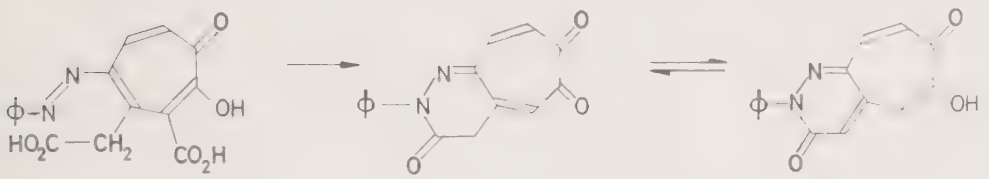
CXXVI CXXVII CXXVIII

Treatment of the tosylhydrazone (CXXIX) of 4-acetyltropolone with alkali also results in cyclization to form (CXXX) and (CXXXI)[95]. The structures of these products were revealed by oxidation experiments.



CXXX CXXIX CXXXI

Cyclization involving an arylazo group on the tropolone ring was also observed by SHEMYAKIN in the following reaction[96]:



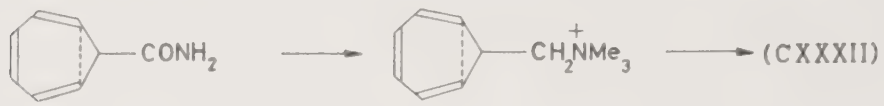
Heptafulvene and its Derivatives

Heptafulvene (CXXXII) is an interesting compound because it is not only the seven-membered analogue of fulvene (CXXXIII) and a methylene analogue of tropone, but can also be considered as the parent structure of azulene (CXXXIV). Its stability has attracted much interest from the theoretical standpoint[97] and its synthesis has

CXXXIII CXXXII CXXXIV

been attempted[98], but it remained unknown until comparatively recently. DOERING and WILEY[16] prepared heptafulvene (CXXXII) starting from norcaradienecarboxamide (CXXXV) which was first reduced to the amine, derived to the quaternary ammonium salt (CXXXVI) and submitted to the Hofmann degradation at room

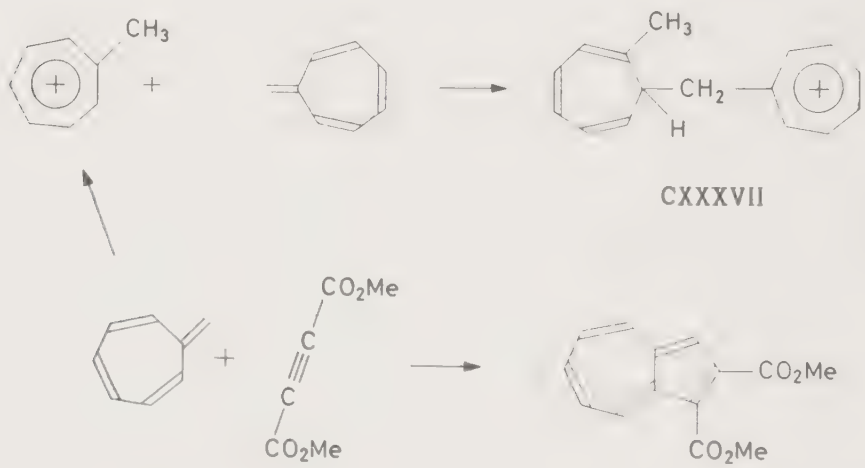
temperature *in vacuo*, the vapour thereby formed being introduced directly into a trap containing cold solvent. The compound (CXXXII)



CXXXV CXXXVI

is an extremely labile red oil which undergoes polymerization even at −80°. Its structure is confirmed by the formation of methylcycloheptane on reduction.

It forms a water-soluble salt (CXXXVII) with concentrated hydrobromic acid and undergoes condensation with dimethyl acetylenedicarboxylate with simultaneous dehydrogenation[12] to give an azulene derivative (CXXXVIII).



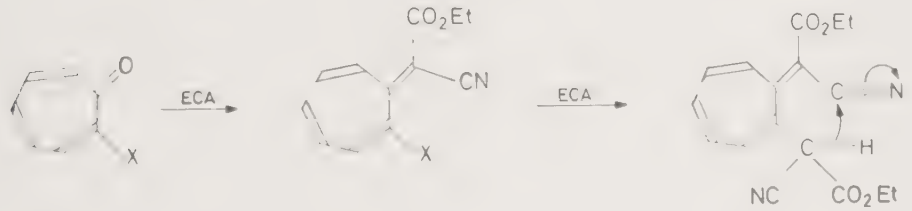
CXXXVII

CXXXII CXXXVIII

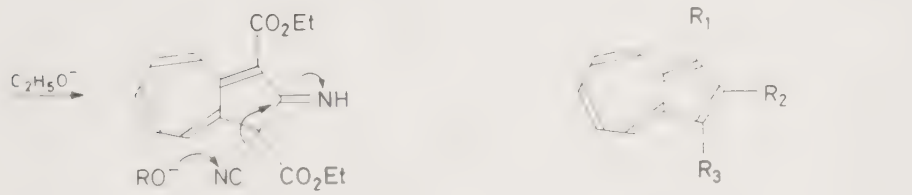
Heptafulvene is known also to be formed, though in a minute amount, by thermal rearrangement of 5-methylenebicyclo-[2,2,1] hept-2-ene (CXXXIX) or methylenecycloheptadienes (CXL), but the product is so labile that it cannot be isolated[99].

CXXXIX CXL

NOZOE and others[100] found that reaction of ethyl cyanoacetate or malononitrile with 2-halo-, 2-methoxy- or 2-tosyloxytropone (CXLI), in the presence of sodium methoxide in the cold, afforded 2-substituted azulenes (CXLII; R_1, R_3 = CO_2Et or CN, R_2 = OH or NH_2) in good yield. For the mechanism of this notable new method for synthesis of azulenes, it was assumed that intermediates like (CXLIII), (CXLIV) and (CXLV) are formed which immediately give the final product (CXLII)[100]. KITAHARA and others[101] found that reaction of malononitrile and tropone also resulted in concurrent condensation and dehydrogenation to form an azulene derivative (CXLII; R_1, R_3 = CN, R_2 = NH_2).

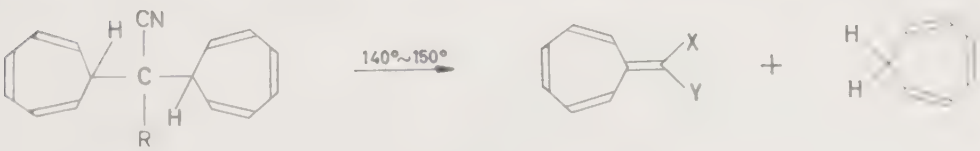


CXLI CXLIII CXLIV



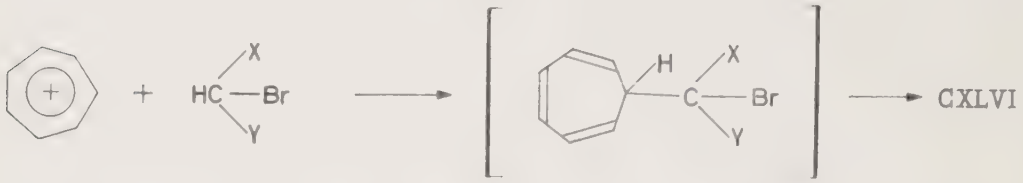
CXLV CXLII

As a means of elucidating the mechanism of the foregoing azulene synthesis, NOZOE and others[102] attempted the preparation of 8,8-disubstituted heptafulvene (CXLVI) and obtained a mononitrile (CXLVI; X = CN, Y = CO_2Et) and a dinitrile (CXLVI; X = Y = CN) by application of bromine, N-bromo-succinimide, or chloranil to tropylmalononitrile or tropylcyanoacetate, as described earlier (see p. 140). The dinitrile (CXLVI; X = Y = CN) was also obtained



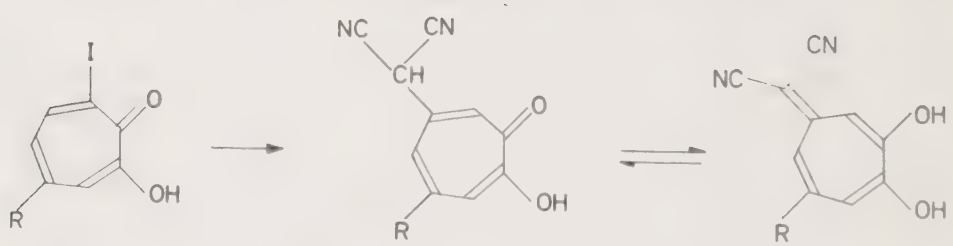
XXIII CXLVI

quantitatively by pyrolysis of ditropylmalononitrile (XXIII; R = CN), together with tropilidene. Diethoxycarbonylheptafulvene (CXLVI; X = Y = CO_2Et) is obtained by dehydrogenation of diethyl tropylmalonate with chloranil[102]. KITAHARA and DOI[101] obtained the dinitrile (CXLVI; X = Y = CN) in good yield by refluxing tropone and malononitrile in acetic anhydride and also found that the heptafulvene (CXLVI: X, Y = CN or CO_2Et) is obtained in one step by reaction of α-bromoderivatives of the active methylene compounds with tropylium ion.



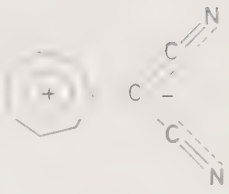
As anticipated, 8,8-disubstituted heptafulvene (CXLVI) afforded 2-substituted azulene (CXLII) by the action of cyanoacetate or malononitrile. The azulene was formed on mere treatment of heptafulvene (CXLVI) with a base. Considering these facts, 8,8-disubstituted heptafulvene would be regarded as the first intermediate in the above-mentioned synthesis of azulenes.

Furthermore, it was found[101] that reaction of potassium amide with 3-iodotropolone (CXLVII; R = H or iso-C_3H_7) in liquid ammonia resulted in the formation of 4-aminotropolone by abnormal substitution; similarly, reaction of malononitrile with the compound (CXLVII) in liquid ammonia gave the compound (CXLVIII), by introduction of a side chain into the 4-position. This compound (CXLVIII) is a dibasic acid and forms a diacetate and mono- and dimethyl ethers. It is clear, therefore, that it has the structure of the 8,8-disubstituted heptafulvene derivative (CXLVIIIb) rather than (CXLVIIIa)[101]. The marked stability of 8,8-dicyanoheptafulvene



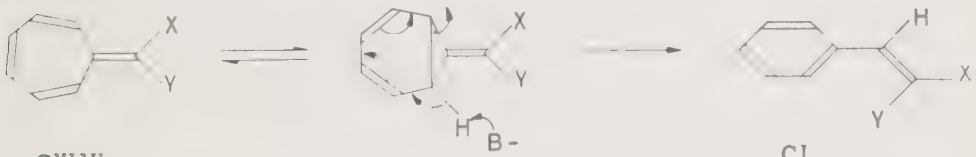
CXLVII CXLVIIIa CXLVIIIb

is probably due to a large contribution of the dipolar structure (CIL). The dipole moment values of dicyano- and cyanoethoxycarbonyl-heptafulvenes are 7·49 and 4·40, respectively[103].



CIL

8,8-Disubstituted heptafulvenes (CXLVI; X, Y = CN or COOEt) undergo rearrangement by the action of a base to form a styrene (CL). Application of acetoacetate or benzyl cyanide to tropylium ion does not produce any heptafulvene derivative, but the styrene derivatives (CL) are obtained[101].



CXLVI CL

Other properties of troponoids which are not discussed in the present chapter include addition reactions (bromine, diazomethane, maleic anhydride), various rearrangements and preparation of new ring systems. It has become quite easy to obtain tropylium ion, tropone and tropolone, and further progress in the study of troponoids and azulenoids is to be expected in the near future.

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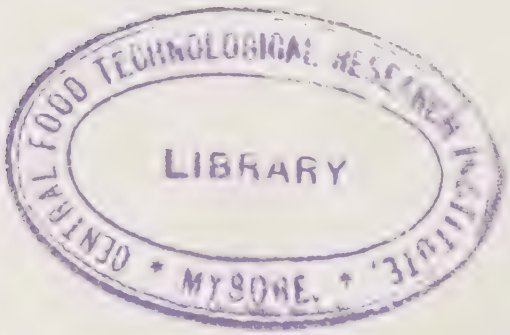
Additions and Corrections in Proof

To page 139 : Another paper on disproportionation of ditropyl ether (IX) to tropone and tropilidene was recently published (Vol'pin *et al.*, *Bull Acad. Sci. U.R.S.S., Otd. Khim.* (1960) 950)

To page 144 : A recent study by Seto *et al.* necessitated a correction of the structure of the compound (LVIII)

To page 155 : 2-Aminotroponethiones (CXVIIIa) are also obtained by the action of phosphorous sulphide on 2-aminotropones[41].

SUBJECT INDEX



P. No.	Due date	Return date
To be issued from 31/9/62		
may pl. be issued to me first		
~~Ramamoorthy 27/8~~ Ramanna 26/8/62		
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B/15 Mr. N.V.N. Moorthy.		
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